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ARCHIVES OF SURGERY

VOLUME 31 SEPTEMBER 1935 NUMBER 3

SLIPPING OF THE CAPITAL EPIPHYSIS OF THE FEMUR IN ADOLESCENCE

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NEW YORK

The cause of slipping of the capital epiphysis of the femur in adolescence is still disputed. Renal rickets, osteomalacia, late rickets, trauma and other causes have been cited.[1] For this reason it was deemed worth while to report three cases in which during operative correction

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From the Laboratory Division, Hospital for Joint Diseases.

1. Whitman, R.: Observations on Bending of the Neck of the Femur in Adolescence, New York M. J. **59**:769 (June 23) 1894. Sudeck, P.: Zur Anatomie und Aetiologie der Coxa Vara Adolescentium, Arch. f. klin. Chir. **59**:504, 1899. Blum, V.: Die Coxa Vara als Belastungsdeformität, ibid. **69**:1065, 1903. Froelich: Beitrag zur Aetiologie der nichtsymptomatischen Coxa Vara, Ztschr. f. orthop. Chir. **12**:80, 1903. Joachimsthal: Die Aetiologie der Schenkelhalsverbiegungen, ibid. **12**:52, 1903. Fittig, O.: Die Epiphysenlösung des Schenkelhalses und Ihre Folgen, Arch. f. klin. Chir. **89**:912, 1909. Elmslie, R. C.: Coxa Vara: Its Pathology and Treatment, London, H. Frowde, 1913. Steindler, A.: Coxa Vara Adolescentium Traumatica, J. A. M. A. **64**:216 (Jan. 16) 1915. Kirmisson, E.: La coxa vara traumatique, Rev. d'orthop. **24**:89, 1913; **26**:240, 1918. Fromme, A.: Die Spätrachitis und ihre Beziehungen zu chirurgischen Erkrankungen, Beitr. z. klin. Chir. **118**:493, 1920. Platt, H.: Pseudo-Coxalgia, Brit. J. Surg. **9**:366 (Jan.) 1922. Wilson, P. D.: Displacement of Upper Epiphysis of Femur Treated by Open Reduction, J. A. M. A. **83**:1749 (Nov. 29) 1924. Key, J. A.: Epiphyseal Coxa Vara or Displacement of the Capital Epiphysis of the Femur in Adolescence, J. Bone & Joint Surg. **8**:53 (Jan.) 1926. Irwin, S. T.: Separation of the Upper Epiphysis of the Femur, Irish J. M. Sc. **1**:71 (Feb.) 1929. Huc, G.: La coxa vara de l'adolescence, Rev. d'orthop. **17**:397 (Sept.) 1930. Klein, N.: Ueber Ossifikationsstörungen beider Hüftgelenke auf endokriner Grundlage, Röntgenpraxis **3**:550 (June) 1931. Taylor, V. J. M.: Displacement of the Upper Femoral Epiphysis, Brit. M. J. **2**:1003 (Dec. 3) 1932. Capener, N.: Two Cases of Adolescent Coxa Vara, Proc. Roy. Soc. Med. **25**: 1077 (Jan.) 1932. Eikenbary, C. F., and Le Cocq, J. F.: Separation of the Upper Femoral Epiphysis, West. J. Surg. **40**:432 (Aug.) 1932. Kienbock, R.: Ueber juvenile Schenkelhals-Malazie hypophysären Ursprungs, Ztschr. f. orthop. Chir. **57**:408 (Oct.) 1932. Brailsford, J. F.: Slipping of Epiphysis of Head of Femur: Its Relation to Renal Rickets, Lancet **1**:16 (Jan. 7) 1933. Fischl, E.: Beobachtungen über die Osteochondritis Deformans Coxae Juvenilis, zugleich ein Beitrag zur Pathogenese der Epiphysenlösung am coxalen Femurende, Arch. f. orthop. u. Unfall-Chir. **33**:456, 1933. Bade, A.: Zur Abgrenzung der verschiedenen Formen von Coxa Vara, Ztschr. f. orthop. Chir. **59**:53, 1933. Wardle, E. N.: Etiology and Treatment of Slipped Epiphysis of the Head of the Femur, Brit. J. Surg. **21**:313 (Oct.) 1933.

sufficient bone was removed for pathologic examination.[2] Particular attention was paid to the epiphyseal cartilage plates and to the head and neck of the femur.

REPORT OF CASES

CASE 1.—A girl 11 years of age complained of severe pain in the region of the right hip for two days prior to admission. Physical examination showed her to be well developed. The right hip joint was in a position of 125 degrees at the angle of greatest extension and in 15 degrees of adduction. Owing to severe pain and spasm clinical examination of the right hip joint could not be done adequately. It was possible to flex the left hip to 90 degrees and to extend it completely. There was, however, but 10 degrees of passive abduction and 25 degrees of passive adduction.

Roentgenograms of the region of the right hip disclosed slipping of the capital epiphysis of the femur (fig. 1 *A*). Roentgenograms of the left hip showed widening of the neck of the femur with compression of the capital epiphysis (fig. 1 *B*). Thus, in addition to the lesion on the right side there existed a healed slipped capital epiphysis on the left.

The condition on the right side (recently slipped epiphysis) was corrected by closed manipulation.[3] A few weeks later, arthroplasty for reconstruction of the

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2. Müller, E.: Ueber die Verbiegung des Schenkelhalses im Wachstumsalter, Beitr. z. klin. Chir. **4**:137, 1888. Hofmeister, F.: Coxa Vara, eine typische Form der Schenkelhalsverbiegung, ibid. **12**:244, 1894. Kocher, T.: Ueber Coxa Vara, Deutsche Ztschr. f. Chir. **38**:521, 1894; **40**:411, 1895. Maydl, K.: Coxa Vara und Arthritis Deformans Coxae, Wien. klin. Rundschau **11**:153, 1897. Sprengel, P.: Ueber die traumatische Lösung der Kopfepiphyse des Femur und ihr Verhältnis zur Coxa Vara, Arch. f. klin. Chir. **57**:805, 1898. Alsberg, A.: Anatomische und klinische Betrachtungen über Coxa Vara, Ztschr. f. orthop. Chir. **6**:106, 1898. Haedke, M.: Zur Aetiologie der Coxa Vara, Deutsche Ztschr. f. Chir. **66**:89, 1902. Schlesinger, A.: Zur Aetiologie und pathologischen Anatomie der Coxa Vara, Arch. f. klin. Chir. **75**:629, 1905. Helbing, C.: Die Coxa Vara, Ztschr. f. orthop. Chir. **15**:502, 1906. Grashey, R.: Coxa Vara Retroflexa Traumatica, Beitr. z. klin. Chir. **70**:186, 1910. Frangenheim, P.: Weitere Untersuchungen über die Pathologie der Coxa Vara Adolescentium, ibid. **72**:239, 1911. Kappis, M.: Klinische und Röntgenologische Dauerergebnisse der Epiphysenlösung am Oberschenkelhals, Zentralbl. f. Chir. **51**:113 (Jan. 19), 1924. Ferguson, A. B., and Howorth, A. B.: Slipping of the Upper Femoral Epiphysis, J. A. M. A. **97**:1867 (Dec. 19) 1931. Camitz, H.: Étude comparée sur la coxa vara dite congénitale et l'osteochondrite coxale juvénile (coxa plana), Acta chir. Scandinav. **73**:521, 1934. Waldenstrom, C. H.: Necrosis of the Femoral Epiphysis Owing to Insufficient Nutrition from the Ligamentum Teres: A Clinical Study Mainly Based on Experiences with the Treatment of Epiphyseolysis Capitis Femoris, ibid. **75**:185, 1934.

3. Jahss, S. A.: Displacement of the Upper Epiphysis of the Femur (Adolescent Coxa Vara) Treated by Closed Reduction, J. Bone & Joint Surg. **29**: 856 (Oct.) 1931. Perkins, G.: The Treatment of Adolescent Coxa Vara, Brit. Med. J. **1**:55 (Jan. 9) 1932. Pomeranz, M. M., and Sloane, M. F.: Slipping of the Proximal Femoral Epiphysis: Therapeutic Results in One Hundred and One Cases, Arch. Surg., **30**:607 (April) 1935.

left hip joint was performed.[4] The bone that was extirpated came to the laboratory in three separate pieces. These were covered by rather smooth, dull articular cartilage. In addition, a fragment of synovial membrane was received which disclosed nothing abnormal on macroscopic or microscopic examination.

On reconstructing the three fragments of bone it was found that they represented most of the capital epiphysis of the femur. This had become flattened and as a result of the mushrooming had extended considerably over the neck, particularly toward the greater trochanter. On gross serial section the epiphysis was seen to bear evidence of being moderately sclerosed, especially beneath the covering cartilage of the portion which fitted into the acetabulum. Toward the greater trochanter the flattened epiphysis was somewhat atrophic. The moderately irregular epiphyseal cartilage plate showed interruptions like those observed in plates which close normally. A few small islets of cartilage-like tissue, apparently connected with the plate, were observed extending into the epiphysis. A portion of the neck of the femur came with the specimen; this was entirely encircled by the epiphysis as by a cuff.

After reorientation of the fragments of bone, seven sections were prepared for histologic examination: section 1 was closest to the acetabulum, and section 7 was nearest the greater trochanter (fig. 1 *C*). The pathologic diagnosis based on macroscopic examination was spontaneously healed or healing slipped capital epiphysis.

Microscopic examination of section 1 revealed compressed epiphyseal tissue. The gliding surface of the cartilage was slightly irregular in certain areas. The trabeculae beneath the cartilage showed nothing unusual. The intertrabecular spaces contained both lymphoid and fatty marrow. The widened, abnormal epiphyseal cartilage plate presented a narrow layer of hypertrophic cartilage cells as well as a thin zone of provisional calcification. The epiphyseal plate showed areas of fibrosis and fibrocartilage. No necrosis of the trabeculae of the epiphysis was seen.

Section 2 disclosed slight roughening of the surface of the articular cartilage. The trabeculae of the capital epiphysis revealed nothing unusual. The head of the femur, however, had been compressed toward the epiphyseal plate. The latter presented an irregular zone of provisional calcification. In some portions of the plate large spaces were filled with blood pigment (fig. 2 *A*). Some of the cartilage of the epiphyseal plate near the pigmented zones had become fibrous.

Section 3 showed the articular cartilage within normal limits. The insertion of the ligamentum teres into the articular cartilage and bone marrow showed nothing unusual except stasis in the capillaries in the subchondral fibrous tissues. The trabeculae of the epiphysis were thickened in some areas without showing evidence of necrosis. The intertrabecular spaces in the epiphysis contained fatty marrow for the most part. The epiphyseal plate was irregular in contour as well as in thickness. In the area marked *a* in figure 1 *C* the plate had buckled or bent on itself so that the proliferating zones were facing each other (fig. 2 *B* and *C*). Small localized areas of degeneration in the form of long slits as well as cysts in the epiphyseal plate were seen. The endochondral ossification was not disturbed to any great extent (fig. 2 *D*). The neck of the femur was covered on its inferior surface by articular cartilage. The trabeculae of the neck were thin and numerous, with no signs of necrosis. The marrow was lymphoid.

4. Kleinberg, S.: Reconstruction: Arthroplasty Operation for Hip, Am. J. Surg. **18**:64 (Oct.) 1932.

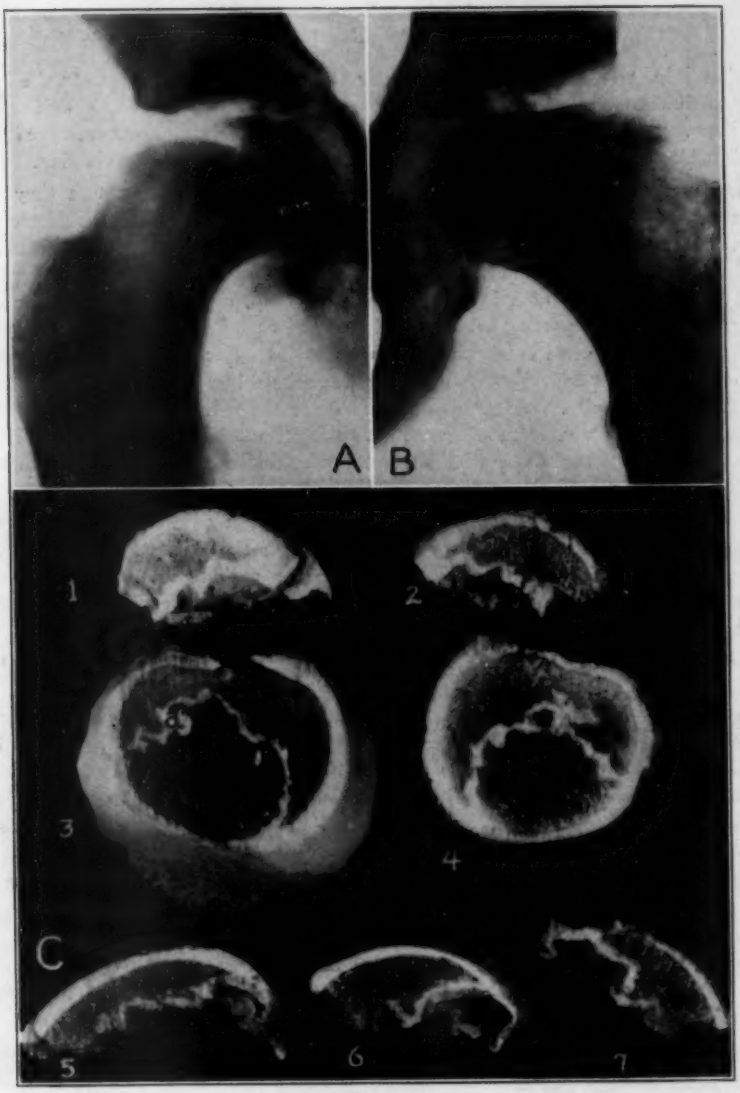

Figure 1

Fig. 1 (case 1).—*A*, slipping of capital epiphysis of right femur; *B*, compression of slipped epiphysis against neck of left femur. *C*, sections from head and neck of left femur. The first section was closest to the acetabulum, and the seventh was nearest the greater trochanter. Area *a* shows buckling in the cartilage plate.

Fig. 2 (case 1).—Sections of original upper epiphyseal cartilage plate. In *A* are cysts, cracks and fibrosis. Considerable blood pigment is seen in cartilaginous defects. Zone of provisional calcification shows herniation into metaphysis. An island of original epiphyseal plate is seen in metaphysis; × 60. In *B* are numerous small cysts and cracks, as well as buckling (*Y*) in epiphyseal plate; × 30. *C* is an enlargement of area *Y* in figure 2 *B*; × 125. Note that proliferating zones face each other. In *D* is a long linear crack in proliferative zone. Endochondral ossification has not been disturbed; × 75.

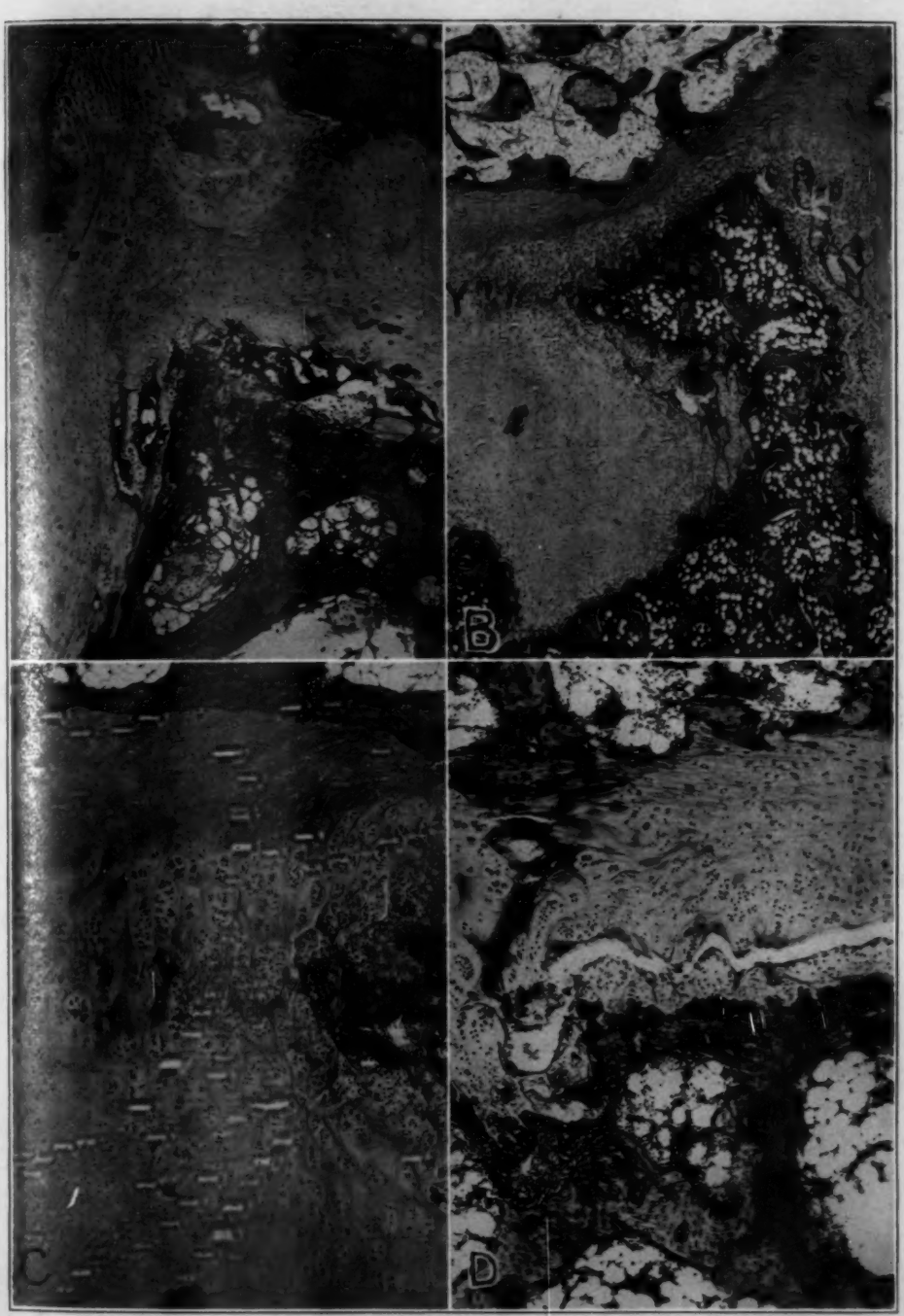

Figure 2

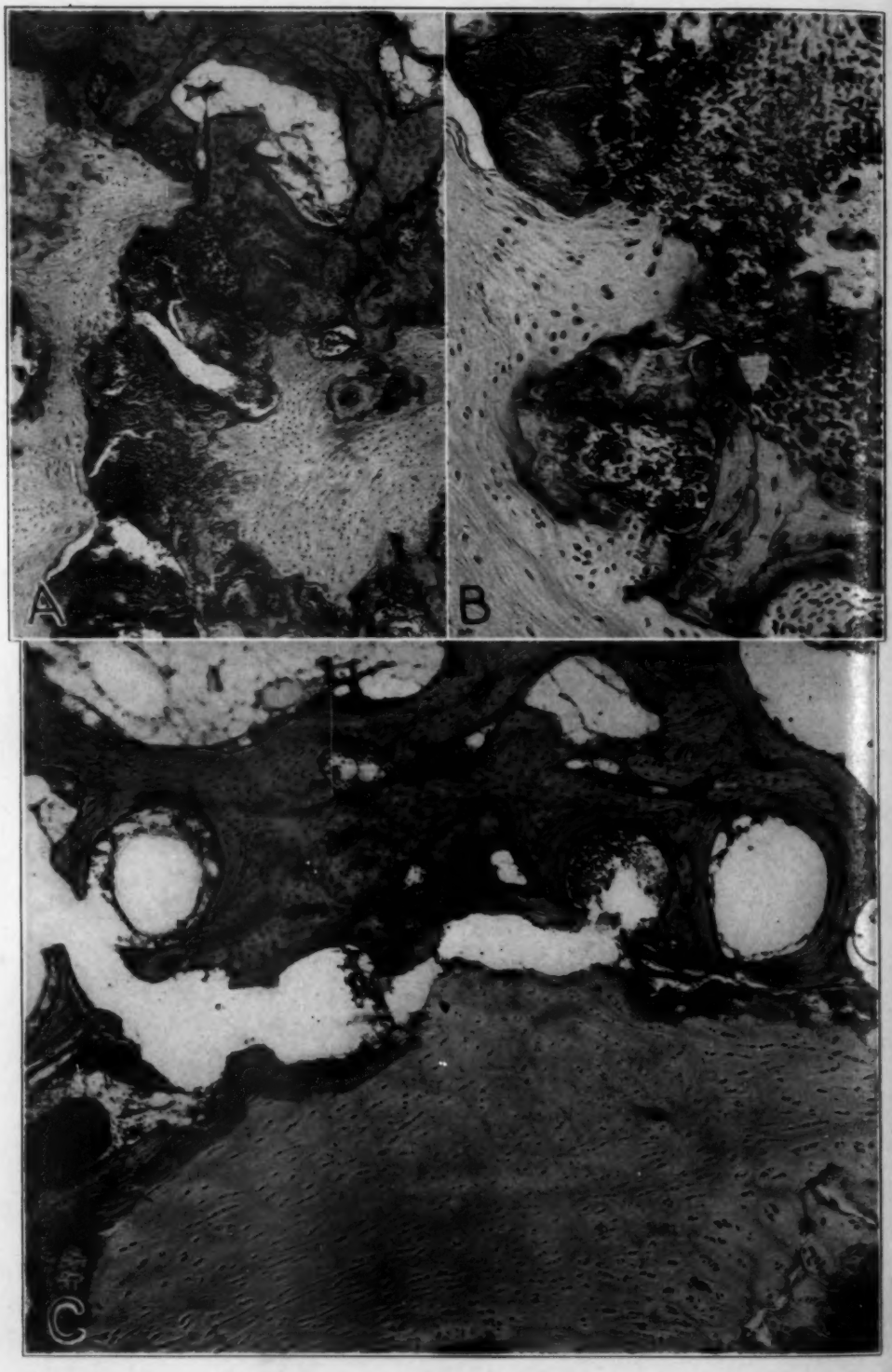

Figure 3

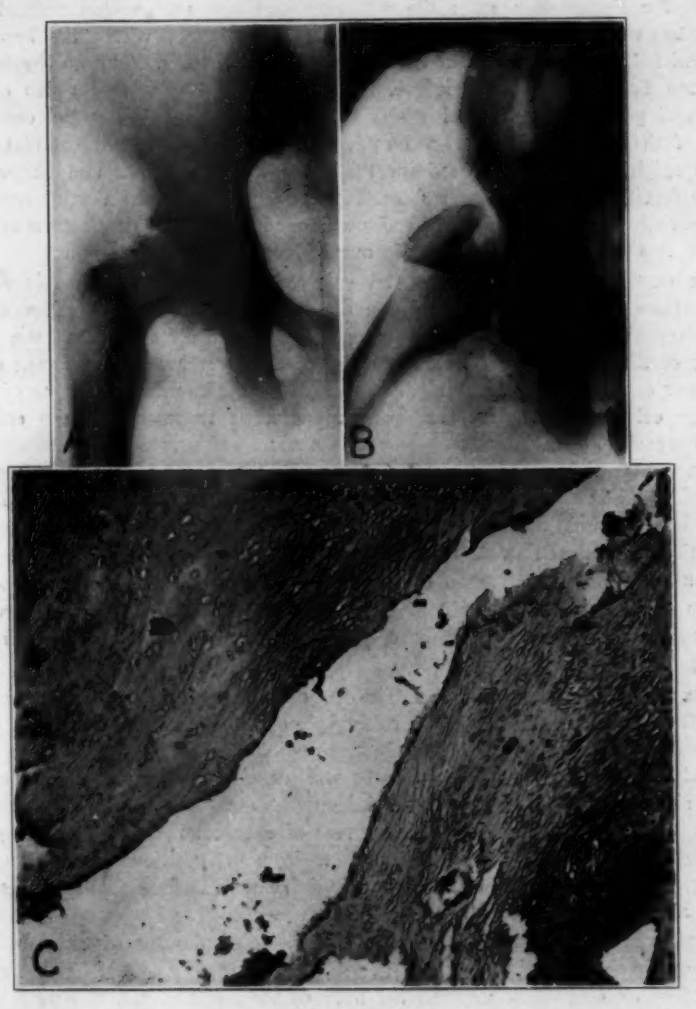

Figure 4

Fig. 3 (case 1).—*A*, islands of displaced original upper epiphyseal cartilage plate in capital epiphysis. Note degenerated areas in cartilage; × 75. *B*, an enlargement of a portion of figure 3*A* showing foreign body giant cells about degenerated areas of cartilage; × 175. In *C*, a linear crack extends from zone of resting cartilage cells through trabeculae of femoral epiphysis; × 75.

Fig. 4 (case 2).—*A*, downward and backward slipping of capital epiphysis and coxa vara of right femur. *B*, nonunion of osteotomized neck of femur (fig. 4*A*) twelve weeks after operation. *C*, a fissure in upper epiphyseal cartilage plate (× 60).

Section 4 revealed that except for some superficial roughening near the insertion of the ligamentum teres the articular cartilage was within normal limits. The intertrabecular spaces of the epiphysis were fibrous where the ligamentum teres existed. The subchondral bone disclosed no necrosis. The epiphysis, which had been flattened to some degree, contained several misplaced areas of upper epiphyseal plate, some parts of which were undergoing endochondral ossification. Some of the displaced degenerated segments of the upper epiphyseal plate in the capital epiphysis were enveloped for the most part by cellular and fibrous tissue and by foreign body giant cells (figs. 3 *A* and *B*). A similar fibrous reaction of the marrow was noted in the distal portion of the epiphysis contiguous to the zone of resting cartilage cells of the original upper epiphyseal plate.

The cartilage plate of the capital epiphysis was irregular in thickness. In certain places it had buckled into the depths of the metaphysis. Several linear cracks containing fibrin and blood were noted in the plate distal to the zone of resting cartilage cells. While small areas of degeneration were present close to the linear cracks, larger areas of degeneration were present in the zone of resting cartilage cells. In one of these cystic areas loose fragments of the epiphyseal plate were seen. An interesting lesion was a microfracture line extending from the zone of resting cartilage cells directly through several of the trabeculae of the capital epiphysis (fig. 3 *C*). Considerable hemorrhage was present. In addition, a healing microfracture of the inferior cortex of the neck was present.

Section 5 disclosed thick trabeculae in the epiphysis. They were closely set and contained few small areas of anuclear bone. There was some fibrocellular reaction in the marrow, which was most marked at the junction between the articular cartilage and the upper epiphyseal plate. Sections 6 and 7 revealed nothing additional.

Case 2.—A boy aged 17 had a limp for one year. Shortly prior to the onset of his illness he had been hit with a rolling-pin on the right leg. For three months afterward he had experienced pain in the region of the right hip while sitting. Physical examination revealed him to be well developed. He walked with a limp on the right side. The right leg was 1 inch (2.5 cm.) shorter than the left. The right leg was held at an angle of 60 degrees of external rotation. It was possible to rotate internally approximately 25 degrees from the position of marked external rotation. Passive flexion of the right hip joint was limited to 90 degrees. No passive abduction was present.

Roentgenograms of the right hip joint revealed downward slipping of the capital epiphysis and slight coxa vara of the femur (fig. 4 *A*). The treatment consisted of an osteotomy through the neck of the right femur. There was nonunion of the fragments after twelve weeks (fig. 4 *B*). At this time the head and portions of the neck of the femur were removed.

The specimen received for study consisted of the capital epiphysis and parts of the neck of the right femur. The articular cartilage revealed nothing noteworthy. A section of the head and neck demonstrated wavy irregular and reduplicated epiphyseal cartilage plates. Dense bone was observed between the broken fragments of the original epiphyseal plate.

Microscopic examination revealed slight roughening of the femoral articular cartilage. The subchondral bone in the head of the femur disclosed a slight increase in the size of the cell lacunae. Osteoblastic activity about the trabeculae in the capital epiphysis was marked. Very little endochondral ossification was present in the localized widened segments of the epiphyseal plate. Other portions of the plate, which were narrow, were undergoing closure. In still other areas fibrinous and cystic degeneration of the plate was prominent. A definite longitudinal split was seen in the epiphyseal plate (fig. 4 *C*).

The diagnosis was tear and degeneration of the epiphyseal plate (in spite of nonunion of the neck, no necrosis of the capital epiphysis was noted).

CASE 3.—A boy aged 12 complained of pain in the right knee which started two weeks prior to his admission to the hospital. Physical examination revealed him to be a tall, obese boy who walked with a marked limp on the right side. Moderate genu valgum was present on each side. The right femur was in slight external rotation; abduction and adduction of that extremity were not limited; internal rotation and hyperextension were limited slightly. A roentgenogram of the region of the right hip revealed slight downward slipping of the capital epiphysis (fig. 5*A*).

Open correction was performed. A segment of bone was removed from the proximal surface of the neck of the femur and from the concave aspect of the loose head. The gross specimen consisted of two segments. The first was composed of a large piece of spongy bone (neck) covered in places with small pieces of cartilage (epiphyseal plate). The second was made up of spongy bone (epiphysis) with underlying areas of epiphyseal plate.

Microscopic examination of the first segment of tissue revealed a tear and degeneration of the epiphyseal plate near the cortex of the neck. Considerable hemorrhage was present (fig. 5*B*). Some portions of the original epiphyseal plate exhibited signs of degeneration, fibrosis, calcification, ossification and marked vascularization of the hyaline cartilage. In other segments of the plate normal endochondral ossification was found. Islands of herniated original epiphyseal plate located in the metaphysis were encircled by degenerated cartilage and necrotic bone. Another histologic preparation revealed abnormal endochondral ossification in the original epiphyseal plate, i. e., endochondral ossification on the epiphyseal and metaphyseal surfaces of the original epiphyseal plate (fig. 5*C*). Examination of the metaphysis revealed edema and fibrosis of the stroma in the marrow spaces. Osteoblastic activity was marked about the trabeculae of bone in the metaphysis (fig. 5*D*). Microscopic sections of the second segment of bone showed changes in the epiphyseal plate and in the marrow spaces of the capital epiphysis similar to those noted in the first specimen (*a*). The diagnosis was tear and degeneration of the capital epiphyseal plate of the femur with healing.

COMMENT

Histologic study of these specimens revealed no evidence of rickets, osteomalacia or specific osteitis fibrosa. The pathologic condition may be interpreted as a fracture through the upper capital epiphyseal plate of the femur and through some of the contiguous osseous trabeculae.

One cannot prove definitely that such a fracture was conditioned on a primary disease of the cartilage plate. Microscopic examination revealed that for the most part the upper epiphyseal plate showed only scattered foci of degeneration, usually close to tears or fractures of the epiphyseal cartilage plate. In these cracks blood pigment was usually present. The buckling of the plate plus the presence of herniated segments of the epiphyseal plate either into the epiphysis or into the metaphysis would tend to support the suspicion that trauma caused many of the microscopic observations. Many of the changes of the original epiphyseal plate, such as fibrosis, calcification and premature

Figure 5

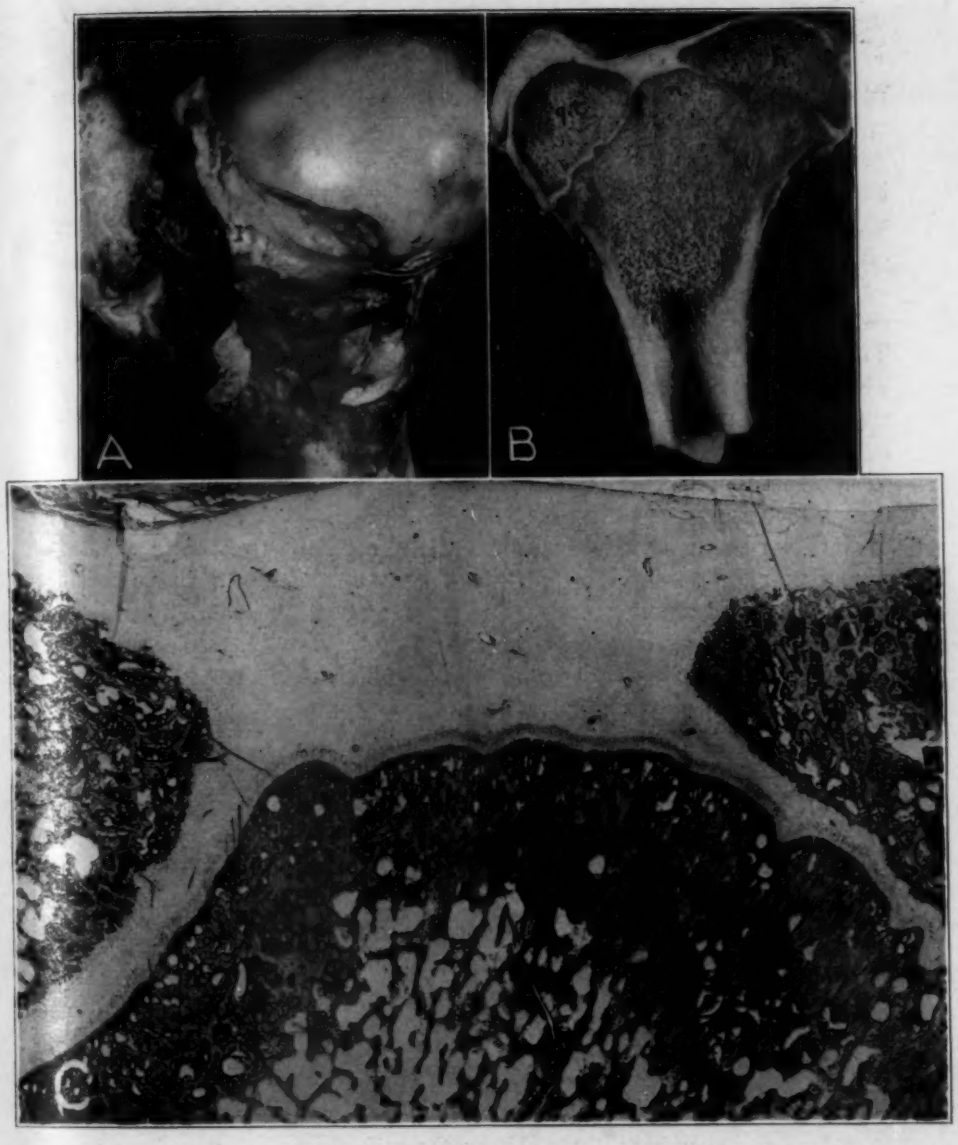

Figure 6

Fig. 5 (case 3).—*A*, slight downward slipping of capital epiphysis of right femur. *B*, irregular fracture in cartilage plate of capital epiphysis. Note focal cystic changes as well as hemorrhage in cartilage (× 50). *C*, endochondral ossification proceeding from epiphyseal and metaphyseal surfaces of upper cartilage plate (× 50). *D*, fibrous bone formation in intertrabecular spaces in metaphysis (× 100).

Fig. 6.—*A*, articular cartilage of head of femur of calf extending over superior surface of femoral neck. *B*, coronal section through specimen shown in figure 6 *A*. Note thick layer of hyaline cartilage covering neck of femur at *n*. Area *h* denotes femoral head and *g.t.*, greater trochanter. *C*, photomicrograph of specimen shown in figure 6 *B*. Note course of epiphyseal cartilage plate and layer of cartilage on superior surface of neck of femur; × 4.

ossification, may be considered as secondary to the fracture of the epiphyseal plate.

The cause of the fracture of the epiphyseal plate can perhaps be best explained by considering, first, the anatomy and the ontogenesis of the femur and, second, the effect of abnormal weight-bearing forces on some of these structures.

In a new-born full term infant no centers of ossification are present either in the head of the femur or in the region of the greater trochanter. The cartilaginous head sits almost directly on the shaft of the femur. The upper portion of a femur in a child from 6 to 12 months old may show a bony center of ossification for the capital epiphysis. The cartilaginous neck, which is very short, is in normal coxa valga. At 3 years of age there is an upward expansion of the shaft corresponding to the neck which causes a tilting of the head. At this time, or occasionally earlier, the center of ossification at the site of the greater trochanter appears. The neck, which is at first entirely cartilaginous, now consists of bone covered on its superior cortex by hyaline cartilage. This layer of hyaline cartilage is continuous with the capital epiphyseal plate and the cartilage encircling the center of ossification at the site of the greater trochanter.[5] At 4 years of age the upper capital epiphysis rests on the entire width of the oblique plate (fig. 7 *A*). A coronal (supero-inferior) section through the head and neck of a normal femur of a child of 4 or more years will show a slight prominence of the inferior angle of the neck (fig. 7 B),[6] which acts as a buttress preventing the capital epiphysis from slipping downward.

Little or no cartilage is normally present on the superior cortex of the neck of the femur of man at or past the age of 4 years.[7] A layer of young periosteum takes the place of the hyaline cartilage. It is important to note that the fibers from this periosteum run in a curved direction into the depths of the matrix of the upper femoral epiphyseal plate (fig. 7 *C*). This allows for direct union between the periosteum and the matrix of the upper epiphyseal plate. The junction between the

5. In animals, such as the rabbit or the calf, the articular cartilage may normally cover part of the superior surface of the femoral neck (fig. 6*A*, *B* and *C*).

6. It is of interest that while in man the medial ossicle of the neck can be seen only when the head and neck are sectioned coronally, Thompson (quoted by Walmsley: J. Anat. & Physiol. **49**:434, 1915) described in the seal a superficial bony prominence which is a continuation of the inferior surface of the neck of the femur to the under-surface of the head. This bony projection in the seal, running onto the head of the femur, is not covered by articular cartilage.

7. Interruption of the continuity of the epiphyseal plate in the neck of the femur is often initiated by the long Sharpey fibers of the attached capsule of the joint.

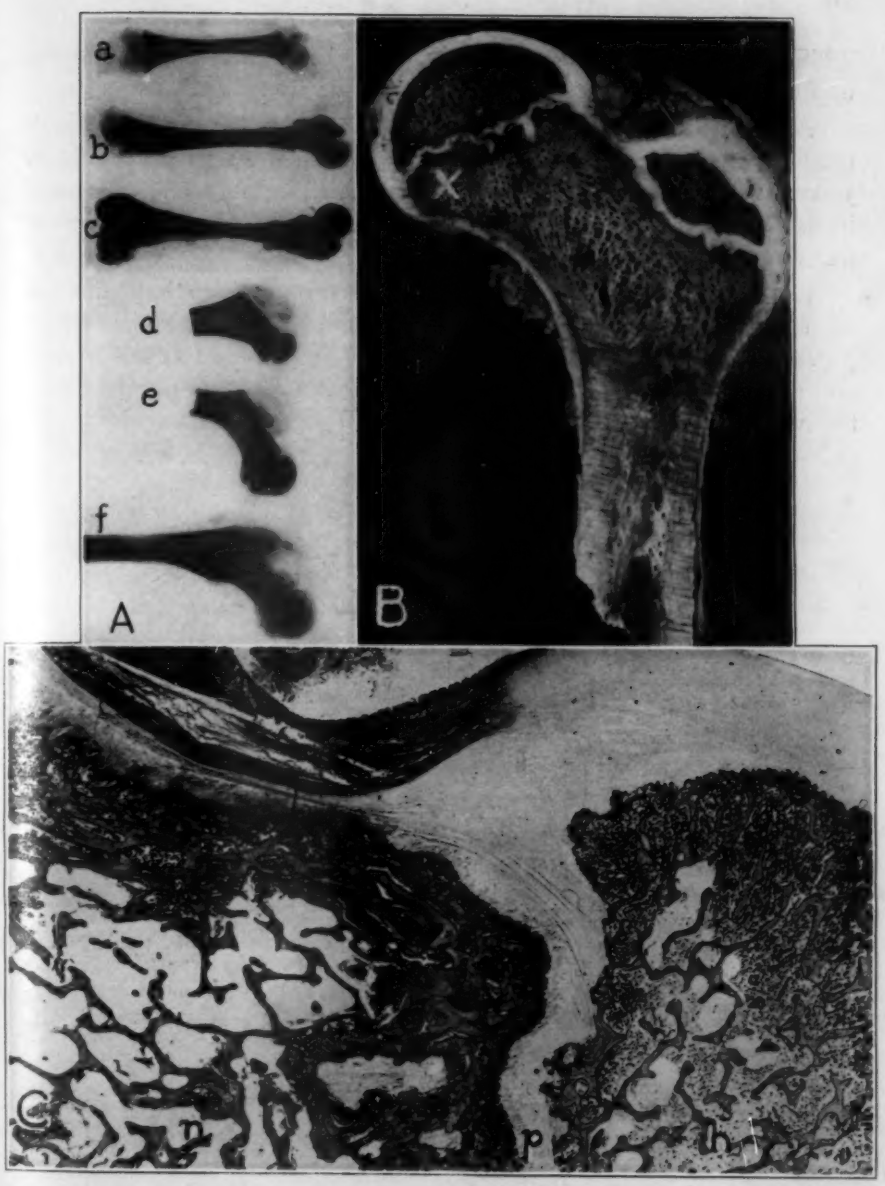

Fig. 7.—*A*, radiograph of proximal portions of femurs of children. Specimen *a* is from a new-born child; *b*, from a child 8 months old; *c*, from a child 18 months old; *d*, from a child 3 years old; *e*, from a child 5 years old, and *f*, from a boy 9 years old. Note inclination of cartilage plate of capital epiphysis. *B*, prominence or buttress (*x*) extending from inferior surface of neck of femur. Coronal section of upper portion of femur from a boy 9 years of age. *C*, photomicrograph showing arched fibers running from periosteum of neck of femur into matrix of upper epiphyseal plate and to contiguous bone trabeculae of epiphysis. *n* indicates neck; *h*, head, and *p*, cartilage plate of capital epiphysis; × 4.

periosteum of the neck of the femur and the hyaline cartilage of the upper epiphysis is a weak area due to "tissue transition."

Additional structural changes exist. The neck increases in length, reaching its maximum ontogenetic size between the ages of 10 and 14 years. The normal coxa valga which is present in the young diminishes in this age period, and slipping of the upper capital epiphysis occurs at this time.

It would seem that the inferior buttress of the neck of the femur and the fibers linking the periosteum to the epiphyseal cartilage plate would prevent the head from slipping. As stated, the normal developmental and mechanical forces at the hip joint tend to produce a normal tilt of the upper epiphysis. Thus, an abnormal weight-bearing force, by

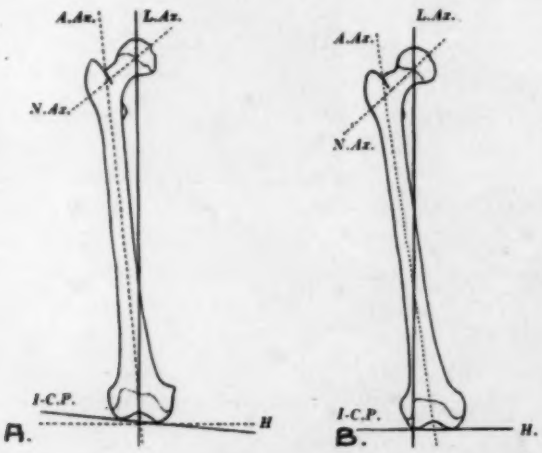

Fig. 8.—*A*, position of femur when feet are apart. The load axis (*L.Ax.*) passes through midcondylar point. Note that the infracondylar plane (*I.-C.P.*) slants upward and laterally. *B*, the load axis passes through lateral femoral condyle when feet are held together. Note that *H*, horizontal axis, coincides with infracondylar plane (after Walmsley).

destroying one or both of the normal barriers, may initiate the slipping of the capital epiphysis.

The weight-bearing forces acting on the hip joint are influenced to a great degree by the forces acting on the knee joint. Walmsley [8] has shown (fig. 8) that the weight-bearing line [9] through the femur passes through the lateral condyle when the patient stands with his feet together. With the feet spread apart, however, the load-axis passes

8. Walmsley, T.: The Vertical Axes of the Femur and Their Relations: A Contribution to the Study of the Erect Position, J. Anat. **67**:284 (Jan.) 1933.

9. The weight-bearing line or load-axis is drawn from the center point of the femoral head perpendicular to the horizontal femoral infracondylar plane.

through the midcondylar point.[10] In the latter position the femur requires additional support, either muscular or otherwise, to overcome the shearing action at the knee joint.

The frequency of slipping of the capital epiphysis of the femur in boys of the Fröhlich type or in girls who are overweight may be due to the presence of an abnormal infracondylar plane. If the muscular support is weak, as is the case in obese boys of the Fröhlich type [11] or in girls who are very overweight, the heavy weight-bearing forces may play havoc on the femoral neck when the femur is in a position which requires additional muscular support. On the other hand, the presence of a longer femoral neck in the tall, thin, growing boy in whom there occasionally develops slipping of the capital epiphysis allows increased leverage action between the shaft of the femur and its neck. Thus, sudden abduction or adduction of the femur with the limb in hyperextension may injure the point of tissue transition on the superior surface of the neck.[12]

It seems possible that a crack or tear at the point of tissue transition on the neck of the femur would follow the course of the fibers of the periosteum into the upper epiphyseal plate. These fibers possibly prevent further progress of the fracture of the cartilage (preslipping stage). Additional trauma probably severs the periosteal fibers which join the upper epiphyseal plate. Additional changes are fracture of the atrophic buttress of the inferior cortex of the neck or compression of that projection. This is only part of the mechanism which initiates the slipping of the capital epiphysis. The activity of the muscles about the hip joint tends to separate the upper epiphysis completely from the neck.

DIFFERENTIAL DIAGNOSIS

Slipping of the capital epiphysis of the femur must be sharply differentiated from secondary coxa vara due to fractures, tumors, cysts or pathologic infiltrations, such as is seen in cases of Gaucher's disease. The congenital type of coxa vara may, if uncorrected in childhood, be mistaken for slipping of the capital epiphysis. In the

10. It has been noted in females that the femoral infracondylar line slants upward and medially when the knees are held together; with the feet apart, however, the line is horizontal. In boys or young men the femoral infracondylar line is horizontal when the knees are held together, and when the knees are apart it slants upward and laterally.[8]

11. Mikulicz, J.: Die seitlichen Verkrümmungen am Knie und deren Heilungsmethoden, Arch. f. klin. Chir. **23**:560, 1879; **23**:670, 1879.

12. Hutchinson, J.: On Detachment of the Epiphyseal Head of the Femur, Arch. Surg. **3**:289, 1892. Poland, John: Traumatic Separation of the Epiphysis, London, Smith, Elder & Company, 1898. Rammstedt, C.: Ueber traumatische Lösung der Femurkopfepiphyse und ihre Folgeerscheinungen, Arch. f. klin. Chir. **61**:559, 1900.

former condition the neck is much more involved than the capital epiphysis; in the latter, changes in the angle of the neck to the femur are secondary to the position of the capital epiphysis.

It is especially important to differentiate Perthes' disease from slipping of the capital epiphysis of the femur. Perthes' disease is characterized by aseptic necrosis of the capital epiphysis without any great disturbance to the epiphyseal plate. Changes in the shape of the slipped capital epiphysis are secondary to mechanical factors and are not part of the disease.

CONCLUSIONS

The tissues removed surgically from three patients with slipping of the capital epiphysis of the femur were examined microscopically. They exhibited evidence that the condition is one of a fracture through the upper femoral epiphyseal plate and contiguous trabeculae of bone. No definite evidence of primary degeneration of the epiphyseal plates was seen. Variations in the weight-bearing forces at the hip joint may be a predisposing factor in the causation of the fracture. The normal tilting of the capital epiphysis, which is the result of normal developmental and mechanical forces, is the basis for the condition.

EXPERIMENTAL SHOCK

THE EFFECTS OF EXTRACTS FROM TRAUMATIZED LIMBS ON THE BLOOD PRESSURE

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AND
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Of the various theories suggested as to the mechanism of traumatic shock, two have recently received most attention, viz: (1) that of the absorption of metabolic toxins from the traumatized area with secondary generalized vasodilatation and increased permeability of the capillaries, a theory advocated by Cannon,[1] Cannon and Bayliss,[2] and others, and (2) that of the local loss of blood or plasma, or both, resulting in a serious decrease in the volume of circulating blood, as supported by the work of Blalock,[3] Phemister and co-workers,[4] Freedlander and Lenhart [5] and others.

Various investigators (Mason and Lemon,[6] Carlson, Woelfel and Powell,[7] Popielski [8] and Bayliss [9]) have shown that extracts of many

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From the Department of Surgery, the University of Chicago.

This study was aided by a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

1. Cannon, W. B.: Traumatic Shock, New York, D. Appleton & Company, 1923.

2. Cannon, W. B., and Bayliss, W. M.: Note on Muscle Injury in Relation to Shock, Medical Research Council, Spec. Res. Ser. no. 26, London, His Majesty's Stationery Office, 1919, p. 19.

3. Blalock, A.: The Cause of the Low Blood Pressure Produced by Muscle Injury in Dogs, Arch. Surg. **20**:959 (June) 1930.

4. Parsons, E., and Phemister, D. B.: Haemorrhage and Shock in Traumatized Limbs, Surg., Gynec. & Obst. **51**:196 (Aug.) 1930. Roome, N. W.; Keith, W. S., and Phemister, D. B.: The Effect of Bleeding After Reduction of the Blood Pressure by Various Methods, ibid. **56**:161 (Feb.) 1933.

5. Freedlander, S. O., and Lenhart, C. H.: Traumatic Shock, Arch. Surg. **25**:693 (Oct.) 1932.

6. Mason, E. C., and Lemon, C. W.: Autointoxication and Shock, Surg., Gynec. & Obst. **53**:60 (July) 1931.

7. Carlson, A. J.; Woelfel, A., and Powell, W. H.: A Possible Hormone Vasomotor Mechanism, Proc. Am. Physiol. Soc., 1908, p. 23.

8. Popielski, L.: Ueber die physiologische Wirkung von Extrakten aus sämtlichen Teilen des Verdauungskanales, Arch. f. d. ges. Physiol. **128**:191, 1909.

9. Bayliss, W. M.: Principles of General Physiology, ed. 4, New York, Longmans, Green & Co., 1924, p. 701.

tissues contain substances which depress the blood pressure, and this fact has been frequently cited[10] in support of the "toxic theory" of traumatic shock. Carlson, Woelfel and Powell,[7] however, after examining saline extracts of a large variety of tissues, found that the extracts of muscle were among the least toxic of the preparations studied. Little attention has been called to the presence in extracts of muscle and other tissues of pressor substances, although the existence of such substances was demonstrated as early as 1898 by Tigerstedt and Bergman.[11] Collip,[12] who more recently studied extracts of a wide variety of tissues, found that both pressor and depressor substances were usually contained in such extracts and that either type of substance could be obtained at will by fractionations with acetone. In fact, by concentration extracts were obtained which when administered to animals caused rises in blood pressure up to 350 mm. of mercury.

The extracts studied by most of the aforementioned investigators were prepared from normal tissues by various chemical extractions. The present experiments were undertaken to determine the effects on the blood pressure of extracts of the muscles of traumatized limbs prepared by rapid mechanical extraction by means of a hydraulic press.

EXPERIMENTAL PROCEDURE

Series 1: Injection of Extracts of Traumatized Muscle into a Jugular Vein.—(*A*) Injection of Uncentrifugated Extracts into a Normal Dog: Six experiments were carried out in the following manner on dogs under ether anesthesia: One hindleg was traumatized repeatedly with a padded hammer until a sustained fall in blood pressure occurred; care was taken to avoid breaking the skin or the bones of the leg. After a period of from forty-five to seventy-five minutes, when the blood pressure remained at levels of from 50 to 70 mm. of mercury, a tourniquet was applied about the traumatized limb at the level of the hip joint, and the limb was amputated approximately 2 cm. below the tourniquet. The skin was removed, and the muscles were dissected from the bones. A large amount of unclotted bloody fluid was invariably obtained during the dissection. This fluid and the muscle tissue were passed through a meat chopper and extracted in a hydraulic press at a pressure of from 350 to 375 Kg. per square centimeter. The extract contained globules of fat and small particles of tissue. In each experiment a second dog was anesthetized with ether and the extract introduced into a jugular vein. Sudden death of the second dog resulted in all the experiments. At autopsy intravascular clotting in the heart and pulmonary arteries was found in four dogs, and pulmonary fat embolism was demonstrated by the gross and

10. Moon, V. H., and Kennedy, P. J.: Pathology of Shock, Arch. Path. **14**: 360 (Sept.) 1932. Cannon.[1] Mason and Lemon.[6]

11. Tigerstedt and Bergman: Skandinav. Arch. f. Physiol. **8**:223, 1898; cited by Collip.[12]

12. Collip, J. B.: A Non-Specific Pressor Principle Derived from a Variety of Tissues, J. Physiol. **66**:416 (Dec.) 1928.

microscopic appearances in the remaining two animals. For this reason the procedure of centrifugating the extract to remove the fat and fragments of solid tissue and the administration of heparin to prevent clotting was adopted in all the subsequent experiments.

(*B*) Injection of Centrifugated Extracts into a Heparinized Dog: In four experiments extracts were prepared by the technic described, and centrifugated to remove the fat and particles of tissue. The top layer of fat was pipetted off and the homogeneous, wine-red middle layer was used for perfusion. In three experiments a second dog was anesthetized with ether and given sufficient heparin (approximately 30 mg. per kilogram of body weight) to render the blood incoagulable; the extract was then introduced into a jugular vein. The reaction of the blood pressure was variable; in one case there was a depression in blood pressure of 36 mm. of mercury, and in two cases there was a rise of 27 and 58 mm. of mercury, respectively. In all the experiments a rapid resumption of the previous "normal" level of the blood pressure occurred in from three to four minutes.

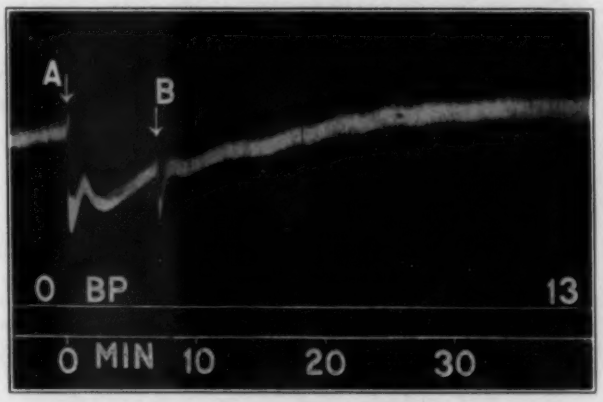

Fig. 1 (experiment 13).—Kymograph tracing showing the effects on the blood pressure of returning to an animal, by vein, the extract obtained from its traumatized leg. The blood pressure was 122 mm. of mercury before the leg was traumatized, 88 mm. when the extract was given (95 cc. was given at *A* and 15 cc. at *B*). The blood pressure fell to 48 mm. but rose again to 88 mm. eighteen minutes after the administration of the first dose of extract and was 113 mm. three hours later.

In one experiment 110 cc. of the extract was injected into the animal from which it had been obtained, heparin being given just before administration of the extract. The blood pressure fell immediately 43 mm.; it then returned in eighteen minutes to the level observed before administration of the extract and in three hours to that existing before traumatism (fig. 1).

The rise in blood pressure on administration of the extract when it occurred in this group of experiments was possibly due to the sudden addition to the blood volume. To test the effect on the blood pressure of the introduction of similar amounts of whole blood, three animals weighing from 10 to 13 Kg. were given by the same method from 225 to 300 cc. of heparinized blood. The blood pressure rose in each from 16 to 35 mm. of mercury and returned to approximately its previous resting level in from six to eight minutes. Thus the pressor effects

caused by the intravenous injection of the extract in some cases were similar to the effects of a transfusion of whole blood. Other factors to be considered as causes of the rise in blood pressure are: 1. The increased production of epinephrine during the trauma and the storage of this substance in the exudate in the leg, with subsequent extraction. 2. The vasoconstrictor properties of traumatized blood, as described by Phemister and Handy.[13] These properties, however, were found by the authors just cited to be inadequate to cause a rise in systemic blood pressure. 3. Effects of temperature, i. e., vasoconstriction due to

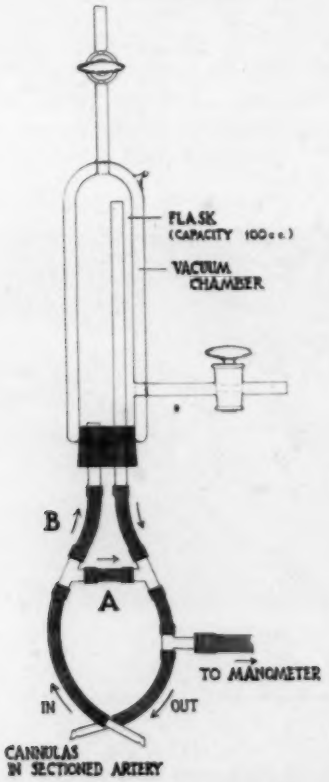

Fig. 2.—Modified Anrep viviperfusion apparatus used for administration of the extract without changes in the volume of circulating blood. The rubber tube is clamped at point *B* and open at *A* during the preparation of the experiment; perfusion occurs when the tubing is released at *B* and clamped at *A*.

the perfusion of cold material. This was ruled out by careful control of the temperature of perfused material in two experiments, in which the rises in blood pressure persisted. 4. The presence of pressor substances in the extract, as described by Collip.[12]

The question as to the effect of epinephrine was investigated and discarded by reason of the following experiments: In two dogs, the adrenal glands were totally excised, and after the animals had a period of rest of from one and a half to two hours, one hindleg of each was traumatized and amputated, and the muscle was

13. Phemister, D. B., and Handy, J.: Vascular Properties of Traumatized and Laked Bloods, J. Physiol. **64**:155 (Nov.) 1927.

extracted as previously described. The perfusion of the extract into a second dog of similar weight by means of a cannula inserted in a jugular vein resulted in both instances in a transient minor depression followed by a considerable rise in blood pressure. The rise in one case amounted to 90 mm. of mercury and was followed by a return to the resting level in from nine to ten minutes. It was then thought that the pressor effect observed in these experiments was due chiefly to the large sudden increase in the volume of the circulating blood or to the presence of pressor substances.

Series 2: Viviperfusion Experiments.—To eliminate the factor of increased blood volume, the following series of experiments was performed, using a modified Anrep viviperfusion apparatus [13] (fig. 2).

Summary of Viviperfusion Experiments

Experiment Number	Weight of First Dog, Kg.	Blood Pressure When Limb Was Amputated, Mm. of Mercury	Weight of Traumatized Muscle Obtained, Gm.	Volume of Extravasated Fluid and Extract, Cc.	Fluid Recovered, Percentage of Calculated† Blood Volume	Weight of Second Dog, Kg.	Changes in Carotid Blood Pressure, Mm. of Mercury (a) On Perfusion of the Total Extract	
15	16.6	65	796	390	31.5	9.6	Plus 26	
16	18.6	70	582	250	18.0	12.1	Plus 8	
17	12.4	50	424	...	....	17.8	Plus 15	
18	9.7	49	440	178	24.6	19.0	Plus 19	
25*	10.75	46	...	...	....	13.9	Plus 17	
							(b) Fractionations	
							Perfusion of Extravasated Fluid	Perfusion of Muscle Extract
19	24.0	46	770	540	30.1	9.5	Plus 17	(Clotted)
20	15.5	68	507	165	14.3	15.5	Plus 11	No change
21	23.0	36	...	...	....	14.0	(Clotted)	Minus 41
22	10.5	41	...	...	....	16.1	Plus 7	Minus 10
23	12.5	36	...	...	....	13.0	Plus 15	Minus 8
24	11.5	50	319	205	24.0	10.84	No change	Minus 5
26	23.2	91	1,189	603	35.0	18.5	No change	Minus 21

* In this experiment adrenalectomy was performed one and a half hours before the dog's limb was traumatized.

† Calculated as one thirteenth of the body weight.

Twelve dogs weighing from 9.7 to 24 Kg. were anesthetized, some receiving ether and a few, sodium barbital administered intravenously. One hindleg was traumatized and amputated when the blood pressure remained at levels of from 36 to 91 mm. of mercury. The muscles were extracted in the hydraulic press as described, with the exception that in seven experiments the bloody fluid which exuded during dissection was removed and the muscles extracted separately.

In each experiment a second dog, usually of similar or lesser weight, was anesthetized with ether or with sodium barbital administered intravenously and given sufficient heparin (approximately 40 mg. per kilogram of body weight) to render the blood incoagulable. An Anrep viviperfusion flask of 100 cc. capacity was then inserted in a femoral artery. The use of this viviperfusion flask permitted the administration of large amounts of the extract without increasing the volume of circulating blood. The general blood pressure was measured and

recorded by means of a cannula inserted in the carotid artery and connected to a mercury manometer, and the blood pressure distal to the perfusion flask was similarly recorded. In three experiments (15, 18 and 21) a plethysmograph was placed on the leg distal to the perfusion flask. In experiment 25 the first dog was prepared by total adrenalectomy one and a half hours before being traumatized, and the experiment was then continued as described.

A summary of the experiments and of the results obtained is given in the table, and typical kymograph tracings are given in figures 3, 4, 5 and 6. In each of the five experiments in which the extract perfused was obtained from the combined bloody fluid and the muscles, there was a rise of the blood pressure of from 8 to 26 mm. of mercury. In the two experiments (15 and 18) of this group

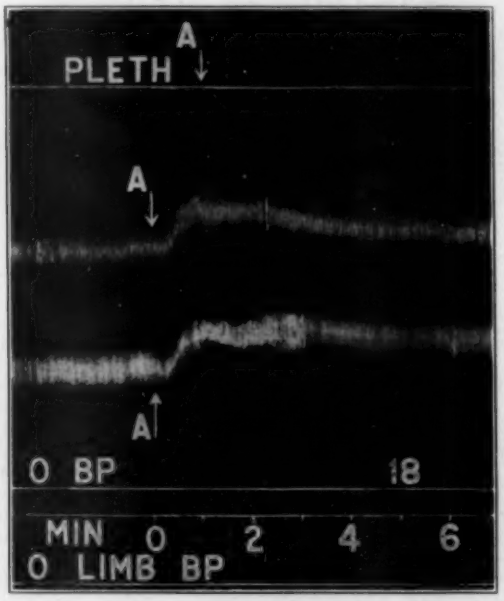

Fig. 3 (experiment 18).—Kymograph tracings showing the effects on the blood pressure of a dog of viviperfusion of the total extract from the traumatized limb of another dog. One hundred cubic centimeters of extract was given at *A;* note that there was a rise in blood pressure of 19 mm. of mercury in both the general blood pressure and the blood pressure of the limb, with a concurrent diminution of the volume of the limb, as indicated in the uppermost curve, marked *pleth.*

in which plethysmographic studies were made, there was a diminution of the volume of the limb simultaneous with the rise in the blood pressure.

In the seven experiments in which the bloody fluid and the extract of muscle were separated, the perfusion of the bloody fluid resulted in a rise of the general blood pressure of from 7 to 17 mm. of mercury in four experiments; no change of general blood pressure resulted in two experiments (in one of which there was a rise of 5 mm. of mercury in the blood pressure of the limb) while clotting prevented taking the measurement in the seventh experiment. In five experiments

Fig. 4 (experiment 19).—Kymograph tracing showing the effects on the blood pressure of viviperfusion of the extravasated bloody fluid from the traumatized limb. Note the rise in blood pressure of 17 mm. of mercury after a preliminary slight depression following the administration of the extract, as indicated by the arrow.

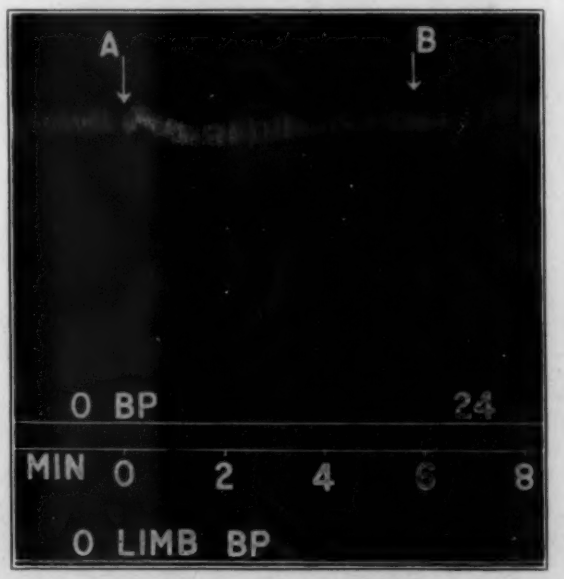

Fig. 5 (experiment 24).—Kymograph tracings showing the effects on the blood pressure of viviperfusion of the extract obtained from the muscles alone from a traumatized limb. Note the slight rise in general blood pressure, as shown in the upper curve, followed by a depression of 5 mm. of mercury, and the more pronounced fall in blood pressure of the limb, as shown in the lower curve, indicating local vasodilatation.

the administration of the extract of muscle alone produced a fall in blood pressure of from 5 to 41 mm. of mercury; no change in the blood pressure occurred in the sixth experiment, and clotting occurred in the seventh. In experiment 21 there was no marked change in the volume of the limb incident on the perfusion of either the bloody fluid or the extract of muscle.

In all cases the alteration of the blood pressure was transient, recovery to the previous level beginning before completion of the perfusion and being complete usually within from five to eight minutes. In no case was there a depression in the blood pressure of any permanence. The results of the experiment in which preliminary adrenalectomy was performed were similar to those of the remaining experiments of the corresponding series.

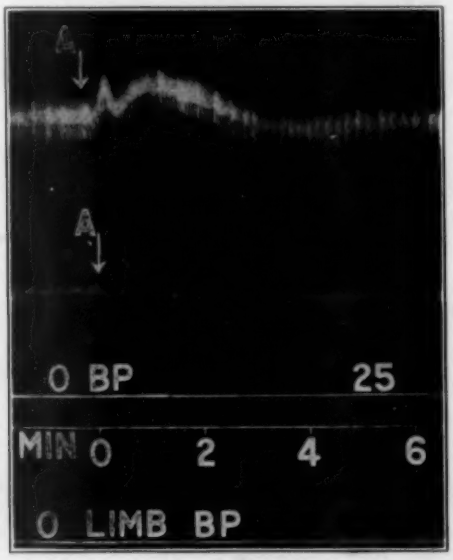

Fig. 6 (experiment 25).—Kymograph tracings showing the effects on the blood pressure of an extract prepared from an adrenalectomized dog. One hundred cubic centimeters of the extract was given at *A;* note the resulting marked biphasic rise in blood pressure.

COMMENT

The extracts of tissue studied by the investigators cited previously were usually prepared by the use of solvents, by boiling or by concentration methods. Many of these extracts have been reported as toxic and were found capable of causing death in some cases. It must be conceded, however, that the methods of preparation were frequently not physiologic and may have been capable of so altering the materials present in the extract as to increase its toxicity. Collip [12] has shown that most tissues contain both pressor and depressor substances, and either type of material can be concentrated and purified at will. In the present experiments

extraction was carried out by means of a hydraulic press, a rapid and entirely mechanical method; hence the concentrations of the various hemodynamic substances would be expected to remain in much the same proportions in the extract as in the original tissue.

The most toxic of the extracts of tissue studied by previous investigators were those of such tissues as lung and liver, while the extracts of muscle were found to be among the least toxic. Yet the toxicity of such extracts has been cited as evidence in favor of the toxic theory of traumatic shock, although cases of large injuries to muscles are the ones in which shock most commonly occurs, and the lungs and liver are seldom concerned. For this reason traumatized muscle was used as the source of the extracts studied in the present experiments, the degree of "shock" induced by the trauma being controlled by direct readings of the blood pressure.

In the first series of experiments it was demonstrated that extracts prepared as described had marked blood-coagulating properties and that this factor was sufficient to kill instantly the animal to which the extract was given by way of a jugular vein, death resulting from intravascular clotting. Also the crude extract was found to contain sufficient particles of fat and of tissue to cause sudden death by pulmonary embolism in several cases. These properties of muscle extracts may be an additional explanation of the "toxicity" observed by certain other workers.

In the final series of experiments the extract was purified by centrifugation; the recipient was heparinized, and the extract was administered by a viviperfusion method, by which alteration of the volume of circulating blood was prevented. In these experiments it was found that the perfusion of a total extract of the extravasated blood and the muscles of a traumatized limb invariably caused a slight transient rise in blood pressure. On fractionation of the extract by separation of the bloody fluid obtained during dissection of the limb, a rise in blood pressure was usually found to occur when the bloody fluid was perfused. When the extract of muscle only was perfused there was a slight to moderate depression in blood pressure in most cases. The depressor responses were of magnitudes similar to those observed with perfusion of extracts of normal muscle. In both groups of experiments the alterations in blood pressure were transient, a return to the resting level occurring within a few minutes; in no case did a permanent depression in blood pressure or death of the animal occur during the period of observation (from two to six hours). Thus only a moderate degree of toxicity was demonstrated for extracts of traumatized muscle prepared in a hydraulic press, and in fact the total extract was invariably pressor in its effect. No support for the toxic theory of traumatic shock can therefore be adduced from these experiments.

The explanation of the rises in blood pressure observed seems to be the presence of the "non-specific pressor substance" studied by Collip,[12]

since the effects of temperature and volume were ruled out by the methods used, and Phemister and Handy [13] could demonstrate no such marked vasoconstrictor effects by the viviperfusion of blood traumatized in vitro. The possibility of excess secretion of epinephrine in the first animal with storage in the limb and subsequent extraction seems ruled out by the results of the three experiments performed after preliminary total adrenalectomy, in which marked rises of the blood pressure occurred. Many of the kymographic tracings showed a biphasic character to the reaction curve of perfusion of both muscle and combined extracts, presumably indicating that these extracts contain a mixture of hemodynamic substances.

A study of the amounts of muscle and of extract obtained (table) showed that from 14.3 to 35 per cent of the total volume of blood (calculated as one thirteenth of the body weight) was recovered from the traumatized limb. Because of the level of amputation and of the losses inherent in extraction not all the fluid lost into the limb was recoverable; hence the total amount of fluid, which appeared to be chiefly blood, is considerably greater than that indicated by the figures given and represents a large local loss from the circulation.

SUMMARY AND CONCLUSIONS

Experiments on dogs are described in which extracts obtained by means of a hydraulic press from the tissues of a traumatized limb were perfused in a second animal. Preliminary experiments indicated that such extracts were markedly hemocoagulant and contained particles of fat and of tissue, and that the extract almost invariably caused death when administered intravenously to a second animal; hence in the final series of experiments the extracts were purified by centrifugation, and the recipient was heparinized.

It was found that the intravenous administration of the total extract (i. e. extract prepared from both the bloody extravasated fluid and the muscles) invariably caused rises in blood pressure in the recipient animal. When the bloody fluid was given alone the rises were again frequently observed, while the use of the extract of muscle alone usually resulted in minor depressions in blood pressure.

It was concluded from these experiments that: 1. Centrifugated extracts of traumatized limbs obtained by means of a hydraulic press caused no depression in blood pressure when perfused as a whole in a second (heparinized) animal; instead, rises in blood pressure occurred. 2. Similar extracts of the traumatized muscles alone (after removal of the extravasated bloody fluid obtained during dissection) were slightly toxic but did not cause a sustained fall in blood pressure or death. 3. The findings do not support the "toxic theory" of the etiology of traumatic shock.

BACTERICIDAL EFFECT OF HIRUDIN AND HEPARIN

II. GROWTH OF ORGANISMS IN BLOOD RENDERED INCOAGULABLE WITH HIRUDIN AND HEPARIN

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AND
ALTON OCHSNER, M.D.
NEW ORLEANS

In another paper,[1] we reported the effects of the application of leeches and of the intravenous injection of hirudin and heparin on bacteremia induced in dogs by the intravenous injection of a suspension of staphylococci. We became interested in this investigation because of the good results we obtained with leeches in the treatment of phlebitis and because of the report by Bosc and Delezenne [2] in which the authors stated that animals are protected from bacteremia by the intravenous injection of hirudin and that in vitro there is an inhibition of the growth of organisms in blood to which hirudin has been added. We conducted both in vivo experiments (on dogs) and in vitro experiments to determine if we could demonstrate such an effect of hirudin on the growth of organisms in blood. Our in vitro experiments are reported in this paper.

EXPERIMENTS

Experiment 1.—Nine sterile test tubes were used. The experiment was conducted under aseptic conditions.

In test tubes 1, 2 and 3 was placed 0.5 cc. of an aqueous solution of potassium oxalate, containing 2 mg. of potassium oxalate per cubic centimeter. In test tubes 4, 5 and 6 was placed 0.5 cc. of an aqueous solution of hirudin containing 2 mg. per cubic centimeter. Five-tenths cubic centimeter of an aqueous solution of heparin containing 0.5 mg. heparin per cubic centimeter was pipetted into each of the remaining three test tubes (7, 8 and 9). In each of the nine tubes was then placed 1 cc. of freshly drawn uncoagulated human blood. One-tenth cubic centimeter of a suspension of staphylococci was added to each tube. The suspension of staphylococci was made by washing the forty-eight hour growth on agar culture plates in physiologic solution of sodium chloride. Each tube was shaken to mix the contents, and all the tubes were placed in an incubator. There was no clotting in any of the tubes. After twenty-four hours the same amount of melted agar

From the Department of Surgery, Tulane University School of Medicine.

1. Ochsner, Alton, and Mahorner, Howard R.: Bactericidal Effect of Hirudin and Heparin: I. Intravenous Injection of Hirudin and Heparin and Leeching in Experimental Bacteremia, Arch. Surg. **31**:308 (Aug.) 1935.

2. Bosc and Delezenne: Imputrescibilité du sang rendu incoagulable par l'extrait de sangsue, Compt. rend. Acad. d. sc. **123**:465, 1896; idem: De l'immunité conférée par quelques substances anticoagulantes. De son méchanisme: excitation de la phagocytose augmentation du pouvoir bactéricide du sang, ibid. **123**:500, 1896.

culture medium at a temperature of 42 C. was mixed with the contents of each tube and then poured into Petri dishes. At the time of this transfer it was noted that a part of the blood in tube 5 had coagulated. This clot in one of the tubes containing hirudin was too small to interfere with the results. The nine Petri dishes were placed in an incubator, and the mixture in them was observed at frequent intervals for eleven days. Whitish irregular colonies were noted on all the plates. Although there was slight variation in the number of colonies in the different areas throughout the plates, the number was approximately the same for each plate. There was no appreciable difference in the rate of growth or the character or number of colonies in the plates containing solutions of potassium oxalate (1, 2 and 3), those containing solutions of hirudin (4, 5 and 6) or those containing solutions of heparin (7, 8 and 9).

The conclusion reached was that the addition of hirudin and heparin does not affect the growth of staphylococci in blood.

Experiment 2.—The experiment was conducted under aseptic conditions. Eight test tubes were used. In each of the first four tubes (1, 2, 3 and 4) was placed 0.5 cc. of an aqueous solution of hirudin containing approximately 1 mg. of hirudin per cubic centimeter. In the remaining four tubes (5, 6, 7 and 8) was placed 0.5 cc. of an aqueous solution of sodium citrate containing 2 mg. of sodium citrate per cubic centimeter of solution. There was no clotting in any of the test tubes. To one of the tubes containing hirudin (tube 1) and one containing sodium citrate (tube 5) was immediately added 0.1 cc. of the suspension of staphylococci. After nine hours, 0.1 cc. of the staphylococcus suspension was added to another of the tubes containing hirudin and 0.1 cc. to one of the tubes containing sodium citrate (tubes 2 and 6, respectively). After twenty-four hours, 0.1 cc. of the staphylococcus suspension was added to another tube containing citrate and 0.1 cc. to a tube containing hirudin (tubes 3 and 7, respectively), and after forty-eight hours, 0.1 cc. of the suspension was added to the last tube containing hirudin and 0.1 cc. to the last tube containing citrate (tubes 4 and 8, respectively). All tubes were kept in the incubator after they were prepared.

Twenty-four hours after the addition of the staphylococcus suspension to each tube, the contents of each was mixed with melted agar peptone culture medium at 42 C. and transferred to a Petri dish. The same amount of medium was used for each tube. The tubes were replaced in the incubator and observed daily.

Colonies appeared in each plate. No difference in the character or the approximate number of colonies was observed between any of the plates containing hirudin and the controls containing sodium citrate.

The conclusion was that hirudin has no inhibitory effect on the growth of staphylococci in blood, even if the organisms are added at various periods up to forty-eight hours after the hirudinization of the blood.

Experiment 3.—The experiment was conducted under aseptic conditions. Twelve test tubes were used (see table). In tubes 1, 2 and 3 were placed 0.5 cc. of physiologic solution of sodium chloride (0.9 per cent) and 0.5 cc. of freshly drawn blood mixed with sodium citrate crystals. In tubes 4, 5 and 6 were placed 0.5 cc. of a solution of hirudin in physiologic solution of sodium chloride and 5 cc. of the solution containing ten crystals of the hirudin.

In three tubes, 7, 8 and 9, were placed 0.5 cc. of a solution of heparin in physiologic solution of sodium chloride, and 30 cc. of the solution containing 3 mg. of heparin. In tube 10 were placed 0.5 cc. of freshly drawn blood and 0.5 cc. of physiologic solution of sodium chloride; in tube 11 were placed, 0.5 cc. of freshly drawn blood and 0.5 cc. of the solution containing hirudin and in tube 12, 0.5 cc.

of freshly drawn blood and 0.5 cc. of the solution containing heparin. To each of the twelve tubes was then added 0.1 cc. of a suspension of staphylococci in physiologic solution of sodium chloride. The contents of each tube were quickly mixed with approximately the same quantity of melted peptone agar culture medium at 42 C. and transferred to a Petri dish. No clotting occurred in any of the tubes, even in tube 10, which was without an anticoagulant. The twelve Petri dishes were placed in the incubator. The type of colonies developing on the plates was the same. They were counted through a square millimeter window at the end of twenty-four and seventy-two hours. There was not enough difference between the average counts and size of the colonies in the different plates to conclude that there was any inhibition of growth on any of the plates. At the end of twenty-four hours, the lowest count for colonies per twenty square millimeters was in plate 9

Table Showing the Results of Experiment 3 from Growing Staphylococci in Hirudinized Blood *

Tube	Contents of Tubes†	Colonies after 24 Hours	Average	Colonies after 72 Hours	Average	Total Average
1	0.5 cc. physiologic solution of sodium chloride; 0.5 cc. citrated blood.....	56-47	51.5	74-58	61	56.25
2	0.5 cc. physiologic solution of sodium chloride; 0.5 cc. citrated blood.....	42-45	43.5	42-36	39	41.25
3	0.5 cc. physiologic solution of sodium chloride; 0.5 cc. citrated blood.....	61-44	50.5	58-57	57.5	54
4	0.5 cc. hirudin; 0.5 cc. citrated blood..	50-39	44.5	56-41	48.5	46.5
5	0.5 cc. hirudin; 0.5 cc. citrated blood..	43-43	43	50-54	52	47.5
6	0.5 cc. hirudin; 0.5 cc. citrated blood..	47-66	56.5	78-45	61.5	59
7	0.5 cc. heparin; 0.5 cc. citrated blood..	39-59	49	74-50	62	55.5
8	0.5 cc. heparin; 0.5 cc. citrated blood..	33-38	35.5	54-46	50	42.75
9	0.5 cc. heparin; 0.5 cc. citrated blood..	22-32	27	47-34	40.5	33.75
10	0.5 cc. uncoagulated blood inoculated with bacteria; 0.5 cc. physiologic solution of sodium chloride.....	66-33	49.5	93-81	87	68.5
11	0.5 cc. uncoagulated blood inoculated with bacteria; 0.5 cc. hirudin.....	41-90	65.5	71-104	87.5	76.5
12	0.5 cc. uncoagulated blood inoculated with bacteria; 0.5 cc. heparin.....	48-65	56.5	100-76	88	72.25

* The preparations used contained 3 mg. of heparin to 30 cc. of physiologic solution of sodium chloride and 10 cystals of hirudin to 5 cc. of physiologic solution of sodium chloride.
† The contents of the tubes were transferred to melted peptone agar culture mediums immediately after the addition of the hirudin, or of heparin, and staphylococci.

(heparin), averaging 27 colonies, whereas the highest count was in plate 12 (heparin) averaging 56.5 colonies.

After seventy-two hours plates 1, 2 and 3 averaged 50.5 colonies per twenty square millimeters; plates 4, 5 and 6 averaged 51 colonies, and plates 7, 8 and 9 averaged 44 colonies. There was an average of 68.5 colonies per twenty square millimeters in plate 10 (without an anticoagulant), but plates 11 (hirudin) and 12 (heparin) averaged 76.5 and 72, respectively.

SUMMARY

In test tubes a suspension of staphylococci was added to hirudinized blood, to heparinized blood, to citrated blood and to blood mixed with physiologic solution of sodium chloride. Three sets of experiments were run, in one the addition of the staphylococci being delayed for periods

up to forty-eight hours after the blood was hirudinized or citrated. In another the blood was incubated for twenty-four hours after the addition of hirudin, or heparin, and of staphylococci before being transferred to the agar plate culture medium. In a third experiment the blood was transferred to agar plates immediately after the addition of the hirudin, or heparin, and the staphylococci.

CONCLUSION

Rendering blood incoagulable with hirudin does not inhibit the growth of staphylococci in blood in vitro.

PURULENT PERICARDITIS

REPORT OF FIVE CASES IN WHICH TREATMENT WAS BY PERICARDIOTOMY, AND REVIEW OF THE LITERATURE FROM APRIL 30, 1927, TO JAN. 1, 1934

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If unrecognized, purulent pericarditis kills the patient. The patient in whom the condition is diagnosed and who is treated expectantly or by therapeutic aspiration fares no better. Operative attack is the only method at one's disposal which offers any chance to cope successfully with the condition.

In spite of a fair percentage of cures from surgical measures, and in spite of the conspicuous reviews of Roberts, Porter, Eliot, Rhodes, Poole and Alexander on the advantages of pericardiotomy when contrasted with the impotence of less radical means, the number of cases in which pericardiotomy is performed for pyopericardium is small. In 1927, we [1] could assemble only 128 cases. Of these, 118 were culled from the literature; 9 were contributed from the surgical services of the University Hospital, and 1 was reported through the courtesy of Dr. Harvey B. Stone.

In view of the not infrequent occurrence of the lesion, we feel that the problem of its treatment is well worth further discussion, especially as no one has had a broad operative experience with the condition. First, we wish, however, to place on record five other cases [2] in which we treated the condition by incision and drainage.

REPORT OF CASES

CASE 1.—A white girl, aged 19 years, was admitted to the Emergency Hospital, Annapolis, Md., March 2, 1929, was operated on, March 7, and was discharged, April 27. She had been sick for a month and very ill for several weeks before admission. Her attack began as one of acute bronchitis followed by pneumonia. An empyema did not develop. A diagnosis of suppurative pericarditis was made because of the character of her breathing and the paradoxical pulse, and because the x-ray picture showed an enlarged pericardial shadow.

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1. Winslow, N., and Shipley, A. M.: Pericardiotomy for Pyopericardium, Arch. Surg. **15**:317 (Sept.) 1927.

2. Four of these cases have been briefly described by Truesdale, P. E.: Low Pericardiotomy for Acute Suppurative Pericarditis, New England J. Med. **208**: 671, 1933 (cases 21, 22, 23 and 24, p. 677).

At operation, 8 ounces (236 cc.) of thin purulent fluid escaped, from which a streptococcus grew out in culture. The operative approach was by the chondroxiphoid route. When the pericardium was opened, pus gushed from the incision. Two tubes for irrigation with surgical solution of chlorinated soda were left in the pericardium for drainage. For several days after the operation, the patient's condition was desperate. On the fourth day irrigations were begun by introducing the fluid into the pericardium through one tube and allowing it to escape through another. Following irrigation of the pericardium, the patient's condition improved.

The girl was a pupil nurse. After several months' convalescence, she returned to duty, finished her training and was graduated. For a year after the operation, she had some shortness of breath when she hurried or climbed stairs but these symptoms eventually disappeared. In May 1934 she was enjoying excellent health and had no manifest cardiac embarrassment.

Case 2.—A white boy, aged 17 years, was admitted to the hospital, April 18, 1930, for cyanosis, shortness of breath and precordial pain of four days' duration. These symptoms followed an attack of scarlet fever which began three weeks before.

Examination disclosed a markedly enlarged cardiac area, an obtuse cardiohepatic angle and a pericardial friction rub at the base of the heart. The cardiac sounds were distant at the apex, but were well heard at the base. The temperature was 102.2 F.; the pulse rate was 120, not paradoxical; the respiratory rate, 30; the blood pressure was 110 systolic and 60 diastolic. The white blood cells numbered 18,100, with a ratio of polymorphonuclears of 78, small lymphocytes 16, and large mononuclears 6 per cent, respectively. A blood culture was negative after seventy-two hours. A diagnosis of pericardial effusion was made. On the morning of April 19, with the patient under avertin anesthesia, a pericardiotomy was done by the combined transsternal and transchondral approach. An incision was made in the midline, extending from the level of the fourth rib to the junction of the second portion of the sternum with the ensiform process and was then curved outward over the edge of the costal margin for 3 inches (7.6 cm.). After the sternum and cartilages were uncovered, an opening was made with a bur through the sternum near its left margin and opposite the cartilage of the sixth rib. The hole was enlarged by rongeur and 2 inches (5 cm.) of the left fifth and sixth costal cartilages was removed. This gave a relatively large exposure through the triangle of safety. The left edge of the pleura was seen, but it was out of the way. The internal mammary vessels did not come into view. When the pericardium was opened, a large amount of seropurulent fluid escaped. It was easy to examine the pericardial sac for adhesions and pockets. A smear of the pus made at the operation showed no organisms, and a culture was negative. A smear made a few days later, however, showed the presence of staphylococci and gram-positive bacilli, and a culture yielded Staphylococcus haemolyticus and gram-positive bacilli. This, of course, may have been a contamination. No drainage was left in the pericardial sac; but several gauze drains were placed down to the opening in the pericardium.

The patient had a stormy postoperative course. His temperature continued high for nine days, ranging from 100 to 102 F., after which it gradually subsided. He has exhibited no signs of subsequent cardiac disability. It was felt that the boy would have had a better convalscence if drains had been put in the pericardium and irrigations had been resorted to.

This patient was operated on under tri-brom-ethylalcohol anesthesia. A relatively small dose was given and was supplemented by a 0.5 per cent solution

of procaine hydrochloride injected under the skin. The combination produced a very satisfactory anesthesia. It offers an advantage over general anesthesia in unruly children and nervous adults, but local anesthesia is preferable when it can be used.

CASE 3.—A 50 year old white man had been desperately sick for several weeks. His illness began as pneumonia in the left lung.

He was seen the day after admission to the hospital at Waynesboro, Pa., in consultation with his physician, who suspected that suppurative pericarditis had developed. The x-ray film, although it showed a large pericardial shadow, was confusing because the opaque area extended far out into the left side of the chest. Paracentesis of the left pleural cavity revealed a pocket of pus in close relationship with the pericardium.

The pericardium was exposed and opened through a chondroxiphoid approach. It contained a large amount of thick pus and a number of adhesions between the layers of the pericardium. There was, also, a walled-off empyema between the left side of the pericardium and the lung just below the hilus and well down on the diaphragm. This was also drained.

The man was in very poor condition when operated on. He had a very low blood pressure and a rapid pulse rate. He died twelve hours after the operation.

Autopsy revealed a chronic empyemic cavity with much thickened walls which were in contact with the left side of the pericardium. We believe that he had the empyema first and that pyopericardium developed later as a complication of the suppurative pleuritis.

CASE 4.—A colored woman, 20 years of age, was operated on at the Baltimore City Hospitals, June 18, 1932, for pyopericardium. She had been ill with pneumonia since May 10. She was short of breath and had a paradoxical pulse; the roentgenogram disclosed a triangular pericardial shadow with the base below and the apex above.

At operation suppurative pericarditis was found. A moderate amount of thick creamy pus was evacuated. Cultures showed growth of a pneumococcus. The operative approach was by the chondroxiphoid route. The woman lived only a few hours after the operation.

CASE 5.—A white man, aged 29 years, was admitted to the hospital, May 22, 1933, with frank pneumonia, type IV, of the right lower lobe of two days' duration. On June 13, a thoracotomy was done for a localized empyema situated high up in the right side of the chest. On culture the fluid from this abscess yielded the pneumococcus. He had an enlarged pericardial shadow, and there was a friction rub in the cardiac area.

These findings, along with an enlargement of the cardiac area, cyanosis, pain in the epigastrium, a slightly paradoxical pulse, a temperature that ranged between 98 and 102 F., a blood pressure of 100 systolic and 60 diastolic, indistinct heart sounds and a white blood cell count of 23,050, indicated that he had the same sort of infection in the pericardium.

Accordingly, four days later, June 17, a pericardiotomy was done under 0.5 per cent procaine hydrochloride anesthesia. An oblique incision was made, extending from about the midline of the sternum downward and outward, parallel to and just above the costal margin. By means of a bur, an opening was made through the sternum over the triangle of safety. With a rongeur the hole in the bone was enlarged to the left, and the bridge of sternum and an inch (2.5 cm.) of the left fifth and sixth costal cartilages were bitten away. The vent exposed a taut pericardium. The surface of the heart lay close to the pericardium. On opening the pericardium, 2 ounces (59 cc.) of a murky serohemorrhagic fluid welled out

of the wound. The incision was made large enough to admit a finger. The surface of the heart was covered with a shaggy and patchy exudate. The pericardial sac was drained with two small rubber tubes. Irrigations were employed for a considerable period. The patient eventually made a satisfactory recovery.

Comment.—This is the only case in the series of 15 cases reported by us in which a patient with combined empyema and purulent pericarditis recovered. Three of the 5 deaths in the series were associated with the combination of empyema and suppurative pericarditis.

REVIEW OF NINETY-NINE CASES

In the present study, we tender an analysis of 99 extra cases [3] in which open drainage has been practiced for the relief of suppurative pericarditis. Ninety-four of these cases have been assembled from the literature. The observations listed in the foregoing pages constitute the remainder of the group. For the most part, these cases have been registered since April 30, 1927, and all of them during the present century.

Sex and Age of Patients.—Fifty-two of the patients were males and 21 were females—a ratio of males to females of 2½ : 1. Twenty-nine of the former, or 58.82 per cent, and 14 of the latter, or 66.67 per cent, recovered. Of the 26 patients whose sex was not recorded, only 6 or 11.54 per cent, recovered. While it is unsafe to make deductions from small series, the figures seem to indicate that the female is the better risk. Nineteen of the 99 patients were between 1 and 10 years of age; 18 between 10 and 20; 19 between 20 and 30; 4 between 30 and 40; 4 between 40 and 50; 2 between 50 and 60, and 1 between 60 and 70. The remainder were designated as men, women or children or were not designated with regard to sex or age. Of the 67 patients whose ages were recorded, 56 were under 30 years of age and 30 were less than 20 years old. Only 11 were over 30 years of age. Thus a large majority of these patients were under 30 years of age and a goodly proportion of them were less than 20 years old. The disease is therefore preeminently one of youth.

Etiology.—In 8 cases the pericarditis was caused by direct implantation of pyogenic organisms introduced from without by bullet or by knife wounds. In 27 cases no mention was made of the source of the infection. In 1 instance, nothing was found to account for the condition. This, however, could hardly have been an example of the idiopathic variety of purulent pericarditis described by some authors, because

3. Three cases attributed to L. E. Vasquez are not included here because the abstract of his article entitled "Suppurative Pericarditis Complicating Bronchopleuropulmonary Diseases" (J. A. M. A. **98**:1042 [March 19] 1932) is lacking in data, and the original paper published in Salvador Médico, San Salvador (**10**:6, 1931), could not be secured.

autopsy revealed a fistulous connection between the pericardium and the left bronchus. In the majority of instances, the pyopericardium was attributed to a metastasis from a distant focus of infection. Osteomyelitis and suppurative processes in other tissues were responsible for 13 of these cases, and diseases of the respiratory tract accounted for 49. Of great interest, in this connection, was the incidence of

TABLE 1.—*Etiology of Pericardial Effusion*

	Recovered	Died	Not Stated	Total
Pneumonia	12	7	0	19
Pneumonia (streptococcic), pleurisy	1	0	0	1
Pneumonia, empyema	5	2	0	7
Pneumonia, empyema, pleurisy	2	1	0	3
Pneumonia (streptococcic), empyema (bilateral) consecutive to thyroidectomy	0	1	0	1
Pneumonia, empyema, suppurative otitis media	1	0	0	1
Pneumonia, pleurisy	0	1	0	1
Pneumonia, abscess of shoulder	1	0	0	1
Pneumonia, infection of upper respiratory tract, otitis media	0	1	0	1
Pneumonia, empyema consecutive to grip	0	1	0	1
Pneumonia, osteomyelitis consecutive to grip	1	0	0	1
Bronchopneumonia, empyema, osteomyelitis, endocarditis consecutive to tonsillitis	1	0	0	1
Bronchopneumonia consecutive to osteomyelitis	1	0	0	1
Empyema (bilateral)	0	1	0	1
Empyema	0	1	0	1
Empyema, osteomyelitis	0	1	0	1
Pleurisy following otorrhea	0	1	0	1
Pleurisy following osteomyelitis	1	0	0	1
Tonsillitis	2	1	0	3
Tonsillitis (streptococcic)	0	1	0	1
Tonsillitis, osteomyelitis	1	0	0	1
Osteomyelitis	1	1	0	2
Chondral abscess	1	0	0	1
Otitis media, jugular thrombophlebitis	1	0	0	1
Abortion, septicemia	0	1	0	1
Pyemia	0	1	0	1
Abscess of nates	1	0	0	1
Infection of arm	1	0	0	1
Erysipelas of face	1	0	0	1
Scarlet fever	1	1	0	2
Extraction of tooth	1	0	0	1
Actinomycosis	0	1	0	1
Epithelioma of lip, with dissection of submaxillary triangles	0	1	0	1
Gunshot and stab wounds	5	1	0	6
Gunshot wound and actinomycosis	0	1	0	1
Wounded by piece of metal	1	0	0	1
None found	0	1	0	1
Not given	6	17	4	27
Totals	49	46	4	99

pneumonia and empyema, either alone or in combination, as a coincidental, primary or secondary process, one or both being noted 42 times. When pneumonia and empyema were both present, the former, as a rule, antedated the latter. Twice, the empyema was overlooked and was discovered first at autopsy. Empyema in association with suppurative pericarditis is a serious combination. Of our 12 patients, 4 had empyema, and of the lot only 1 patient recovered. In 22 of the 99 cases constituting this series empyema was recognized and was drained, with 13, or 59.09 per cent, recoveries and 9, or 40.91 per cent, deaths.

Bacteriologic Examination.—Bacteriologic examination of the pus was made in 53 of the cases. In 5 instances, the culture was sterile. The exudate was thrown away by mistake in another instance. While scattered other organisms were mentioned, the chief offenders were the pneumococcus, 21 times, or 39.62 per cent; the staphylococcus, 12 times, or 22.64 per cent, and the streptococcus, 12 times, or 22.64 per cent. Death occurred in 38.09 per cent of the purulent pneumococcic group; in 25 per cent of the staphylococcic, and in 50 per cent of the streptococcic group. It is not safe to generalize, however, from such a small series. In our first series, the death rate in the pneumococcic

TABLE 2.—*Results of Bacteriologic Examination*

	Recovered	Died	Not Stated	Total
Pneumococcus	11	6	0	17
Pneumococcus, type I	0	1	0	1
Pneumococcus, type I and gram-positive coccus	1	0	0	1
Pneumococcus, type II	1	0	0	1
Pneumococcus, type IV	0	1	0	1
Staphylococcus	2	2	0	4
Staph. pyogenes-aureus	4	1	0	5
Staph. pyogenes-aureus-haemolyticus	1	0	0	1
Staph. pyogenes-albus	1	0	0	1
Staph. pyogenes-aureus and gram-positive bacillus	1	0	0	1
Streptococcus	1	1	0	2
Str. nonhaemolyticus	1	0	0	1
Str. haemolyticus	1	4	0	5
Str. haemolyticus, Bacillus mucosus-capsulatus and a gas-forming anaerobe	0	1	0	1
Str. haemolyticus, gram-negative and gram-positive cocci in short chains	1	0	0	1
Str. haemolyticus and gram-positive bacillus	1	0	0	1
Str. later, at first gram-positive bacillus and cocci	1	0	0	1
Bacillus influenzae	0	1	0	1
Diverse organisms	1	0	0	1
Unidentified organisms	0	1	0	1
Culture sterile	3	2	0	5
Pus thrown away by mistake	0	1	0	1
Not stated	17	24	4	45
Totals	49	46	4	99

group was 37.03 per cent; in the staphylococcic, 53.8 per cent, and in the streptococcic, 30.8 per cent. These figures give for the two series about the same percentage of deaths in the pneumococcic type, but the mortality rate in the streptococcic and staphylococcic types is reversed.

Diagnostic Puncture.—Diagnostic aspiration is valuable only when fluid is obtained, but it should also be remembered that pericardiocentesis, even in the presence of pus, may yield a dry tap (Massart and Béchet, Goinard). For this reason it may prove a hindrance rather than an asset. Such an experience by tending to upset an otherwise well established diagnosis made Coutts momentarily hesitate about sanctioning operative relief. Many authorities, however, unequivocally condemn the use of the aspirating needle on the grounds (1) that it is too hazardous and (2) that it is unnecessary for the making of a correct

diagnosis in the presence of the characteristic physical signs and roentgenographic evidence. If in doubt as to the nature of the disease, it is much safer, they claim, to cut down onto the pericardium and to enter this structure under direct vision rather than to insert a needle blindly into the chest with the possibility of entering the pleural cavity and thus instituting an empyema or of puncturing the heart and causing hemorrhage. Fortunately the latter accident is relatively rare, and, if it does occur, it is ordinarily quite innocuous. When paracentesis pericardii has been definitely decided on, Pincoffs advises that the needle should be introduced close to the sternum through the lowest possible intercostal space on the left side, with its point directed slightly downward and laterally so as to parallel the ventricles. In this connection, the situation of the heart, when the pericardium is more or less full of fluid, is of some moment. Bréntano declares that in all pericardial effusions the heart lies most often right against the anterior wall of the sac even if adhesions are not present, and that in many cases there will be a fusion between the pericardium and the anterior wall of the heart. This means that the heart is liable to be punctured unless great care is exercised on the introduction of the needle. In all of our cases the exudate had pushed the heart forward, where it lay in juxtaposition to the pericardium.

In this series diagnostic puncture was practiced on 47 patients without injury to any vital structure. In contrast, however, to these figures, West and others have reported this accident. In view of these adverse experiences we feel that the procedure is contraindicated, especially as it is not necessary for localization as in thoracentesis. No aspiration was done in 7 cases, including our 5 observations. In 45 instances the report failed to mention whether the procedure was or was not employed. To avoid the hazards attendant on aspiration, slight as they appear to be, we prefer to expose the pericardial sac rather than to run the chance of injury to the heart, the pleura, the intercostal vessels, the coronary vessels or the peritoneum.

Pus.—In the large proportion of cases, the pus had collected behind the heart and had pushed this organ forward directly against the anterior pericardial wall. In a few instances, the heart was attached to the pericardial sac by firm adhesions. Usually it was closely approximated to the pericardium, but, on rare occasions, a thin layer of pus was interposed between these structures. Accordingly, paracentesis is inadvisable, as there is considerable danger of injuring the heart. The amount of pus recovered varied from a few drachms to as much as 2,500 cc. Often the exudate was under high pressure. It was described as foul, yellow, turbid, serohemorrhagic, sanguinopurulent, blood-tinged, thick, fetid, thin, cloudy, creamy, chocolate, liquid, greenish, murky, yellowish green. While in case 5 of our present series, the

fluid evacuated was not actually purulent, it was potentially purulent, for it contained a pyogenic organism, the pneumococcus, and the discharge promptly changed to pus soon after free drainage had been established. Other observers have had the same experience.

In this connection, it is well to remember that it is not the amount of pus that causes the embarrassment to the circulation, but the rapidity with which the effusion occurs. The auricles will tolerate a degree of pressure from a slowly increasing exudate that they could not withstand from a rapidly accumulating effusion. It is in the latter group that prophylactic aspiration has a field of usefulness by releasing the pressure on the auricles and by keeping the patient alive until such time as his condition will warrant the institution of more radical measures.

Symptomatology.—The signs and symptoms are inconstant with a few exceptions. One would expect the heart sounds to be indistinct, and many reports state this as a fact, but the apex of the heart is usually found lying against the anterior layer of the pericardium, and this may give a misleading clearness and nearness to the sounds of the heart. The pulse is usually quickened and the heart action weakened. The few records of blood pressure that are reported show that the pressures were low. Shortness of breath and cyanosis are commonly present. A pericardial friction rub is a fleeting and uncertain sign owing to the fact that the pericardial surfaces are seldom in contact. The paradoxical pulse is fairly constant, but it is not always present. Bulging between the cartilages may be observed in children when there is a large effusion, but this sign is not often encountered. The usual symptoms of sepsis are always present to a varying extent—fever, sweating, exhaustion, leukocytosis.

The outstanding symptoms are those of a septic process associated with cardiac distress and shortness of breath, alterations in the quality of the heart sounds and enlargement in the area of cardiac dulness. In clinching the diagnosis, the most useful confirmatory help is the x-ray film. Ordinarily the shadow of the heart is triangular with the base up, and the outline of the heart is quite clearcut. The apex is seen to the left of the sternum, and the shadow of the apex is rather narrow. In pyopericardium there is a broadening of the pericardial shadow downward. If the effusion is abundant, the shadow is distinctly characteristic and is spoken of as bottle-shaped; but, if the amount of pus is small, the x-ray film may not be so helpful.

Diagnosis.—Inasmuch as the symptoms are inconstant, a correct diagnosis depends largely on the recognition of those diseases of which pyopericardium is a complication. When a patient suffering with empyema, abscess of the lung, osteomyelitis or suppurations within the abdomen continues to be ill after the institution of adequate drainage,

purulent pericarditis is one of the complications that should not be overlooked. Then with a careful routine examination of the chest, supplemented by a roentgenologic study and, if necessary, by a paracentesis pericardii, no great difficulty should be experienced in arriving at a proper conclusion.

In this series of 99 cases, the diagnosis was made before operation in 64 instances; in 3, after opening the chest for the evacuation of a supposed empyema; in 1, by accident, after the resection of a diseased costal cartilage. In 1 case, on entering the pleural cavity, a knife blade was found to have penetrated and to have infected the pericardium. In 30 instances the time of the diagnosis was not mentioned.

Primary Operative Results.—Of the 99 patients, 49, or 49.49 per cent, recovered; 46, or 46.47 per cent died. In 4 cases, or 4.04 per cent, the outcome was not mentioned.

According to Rhodes, the death rate in patients not operated on or treated by therapeutic aspiration is 100 per cent. On comparison of these figures, the superiority of pericardiotomy is indisputable in that it offers a salvage of 50 per cent against, at best, only sporadic cures by other kinds of treatment.

A resection of a costal cartilage or of a rib was done in 43 cases; 24, or 55.81 per cent, of the patients recovered, and 19, or 44.19 per cent, died. According to the individual preference of the surgeon, the costal cartilages from the third to the seventh rib on the left side and from the fourth to the fifth on the right side were selected for this purpose, but the left fifth and sixth ribs were the ones most often excised.

In this series, an intercostal space was not used as an avenue of approach to the pericardium in a single instance. In the remaining 56 cases, the operation was performed by the transsternal route 3 times, with 2 cures and 1 death; once by a posterior approach, with death; once by the trap-door method, with cure; once by the "usual operation," with cure; thrice the condition was discovered by accident, with 2 cures and 1 death; 6 times by the insertion of a trocar and by the institution of continuous drainage, with 1 cure and 5 deaths; on 14 occasions by the epigastric route either with or without resection of one or more costal cartilages, with 8 recoveries and 6 deaths. In 21 operations which were not described, 6, or 28.57 per cent, of the patients recovered; 11, or 52.38 per cent, died. In 4 cases, or 19.05 per cent, the result was not given. In 6 cases, 2 operations were necessary, with 4 recoveries and 2 deaths (Bransfield, Hilse, Loucks, Sherwood, Truesdale, Heuer).

Truesdale favors the extreme lateral and most dependent area of the pericardium as the point of election for drainage. In the second

of his 2 cases he employed this procedure after having failed to evacuate the pus satisfactorily by a resection of the left fourth and fifth costal cartilages. In this instance, the pericardium was adherent to the pleura, which permitted the sac to be drained without the pleural cavity being traversed. Certainly, such favorable conditions would not ordinarily prevail. On the whole, we feel that the best approach for the operative relief of purulent pericarditis is the costoxiphoid route with resection of the left seventh, sixth and fifth costal cartilages together with a portion of the sternum, if this is found necessary. At any rate by affording more room, this procedure adds greatly to the comfort of the surgeon and lessens rather than increases the operative hazards.

The probability of the patient's recovery, however, seems to depend more on the etiology of the lesion than on the method by which the pericardium is attacked. There were 8 cases of gunshot or stab wounds, with cures in 75 per cent (one of the deaths, that in case 44, cannot rightly be attributed to the pyopericardium, which had healed when an actinomycosis developed elsewhere from which the patient eventually died; the other death, that in case 45, was the result of exsanguination from repeated small hemorrhages); 49 cases of respiratory lesions with cures in 59.18 per cent, included in this group, were: 39 cases of pneumonia, with cures in 64.10 per cent; 1 of pyemia, with a fatal outcome, and 8 in the osteomyelitic group, with cures in 25 per cent.

Open drainage at the earliest possible moment appears to be the best way of handling this malady. Unfortunately, a careful analysis of the available material is not in accordance with this view, for of the 55 patients operated on from a few days to four weeks after the onset of symptoms, 37, or 67.28 per cent, recovered and 18, or 32.72 per cent, died; of 39 patients operated on within five days, 24, or 61.54 per cent, recovered and 15, or 38.46 per cent, died; of 16 patients operated on after five days, 13, or 81.25 per cent, recovered and 3, or 18.75 per cent, died. In spite of these figures we feel that early operation is the better plan to follow, because pus on general principles should be evacuated at the earliest possible moment.

In this connection, Klose and Strauss voice the opinion that it is best to operate before the exudate has changed to pus. They claim that suppurative pericarditis may be prevented, even in the presence of pyogenic organisms, if such a policy is adopted, and they furnish as substantiatory evidence the report of a case in which they operated in this stage with success. Both our experience and that of Brooke seem to support this contention. Brooke claims to have cured 2 patients by pursuing this policy. In case 7 of our first series, the fluid was hemorrhagic and the patient recovered satisfactorily. In case 82 of our second series, the exudate was a murky hemorrhagic fluid which contained

in culture type IV pneumococci. This patient also recovered. Here, then, are 5 cases in which the effusion was infected but nonpurulent and in which all of the patients recovered. The question naturally arises, should this be the line of treatment invariably pursued in cases of exudative pericarditis potentially purulent? The evidence seems to warrant such a policy, but the answer must await further confirmation. These are desperate cases, and anything that holds the promise of a definite lessening in the mortality rate should be given an extended trial.

Our investigations lead us to believe that if the patient is in bad shape, a reasonable delay in the institution of pericardiotomy does not materially compromise his chances for recovery.

When the disease has become fully established, it appears that the only hope for lowering the mortality rate is the early recognition and the prompt evacuation of attendant purulent foci. No matter how well or at what stage pericardiotomy is performed, it fails to succor if an abscess in the pleural cavity is overlooked, or if secondary collection of pus in the pericardial sac escapes detection. Occasionally a secondary intervention may be found necessary to relieve a pocketing of the pus, for better drainage, or to prevent blockage of the drainage tube. Among the 99 instances herein collected, this happened 3 times, namely, once each in cases reported by Hilse, Loucks and Truesdale, with 2 recoveries and 1 death. If the avenue of approach does not permit proper drainage of the pus, another route may have to be adopted. For example, Bransfield, after the resection of the left fourth costal cartilage with the recovery of only 1 ounce (about 29 cc.) of pus, suspected that the pericardial sac had not been thoroughly emptied. He thereupon excised the left fifth and sixth costal cartilages with the release of one-half pint (about 236 cc.) of fluid and cured his patient. Heuer on resection of the left fifth costal cartilage found the heart in direct contact with the pericardium and adherent to it. Efforts to free these structures had to be stopped because of damage to the cardiac musculature. Heuer turned the patient on his side and excised a rib in the posterior axillary line so as to permit an approach to the pericardium from behind. The lung was found to be adherent to the parietal pleura. Accordingly a needle was thrust through the lung into the pericardial sac, and thin pus was withdrawn. The lung was, therefore, penetrated with a blunt instrument, and tube drainage was instituted. The patient was cured of his pyopericarditis, but died six months later of an actinomycosis of the dorsolumbar region. Sherwood by accident entered the pleural cavity. He met the situation by the insertion of a gauze pack into the wound. Two days later he opened the pericardium with a cautery, and cured his patient. Miller resected the fifth costal cartilage, inserted a gauze pack, and twenty-four hours later incised the pericardium, with

recovery of the patient. Adye-Curran and Buermann released the contents of a postoperative encysted abscess by puncturing the wall of the pocketed pus with a finger introduced through the original wound.

On occasion, the heart has been noticed to cease beating when the pericardium was incised. This peculiar phenomenon, spoken of as cardiac "standstill," occurred in cases reported by Harrigan, Metivet, and Ljunggren. In Harrigan's case, the temporary arrest of the heart was relieved by the placing of the drains. Metivet had a strikingly similar experience. With the injection of epinephrine hydrochloride into the cardiac musculature, pulsation returned, but ceased permanently in half an hour. Ljunggren also reported a heart block which behaved precisely like those in the preceding two cases. The heart lay motionless in its sac, but on compression of the left ventricle it began to pulsate again.

On rare occasion the pericardial effusion has been evacuated through the left pleural cavity. In most of these cases a thoracotomy had been performed for a supposed pleural exudate, but a distended pericardium was found to exist instead and was drained through the original wound (Colwick, Magie). West, Savory, Lane and Steward and Garrod have also recorded cases illustrative of this mistake. Cochez and Fenouillet, after the resection of a diseased cartilage and rib, saw pus issuing from a vent in the bed of the operative field. While performing débridement of this area, they discovered that the fistula pierced the pericardium.

While the closed method of emptying pus from the pericardial cavity, as devised, described and practiced successfully by Whittemore, may not come strictly under the head of pericardiotomy, it is nevertheless akin to that procedure in that the surgeon exposes the pericardium through an open incision before he punctures the wall of the pericardium with the trocar. This procedure is applicable, however, only before large masses of fibrin have formed; otherwise some one of the open operations must be employed.

In the present series, the closed type of drainage was practiced 7 times, with cure in 1, or 14.29 per cent of the cases, and death in 6, or 85.71 per cent. While the number of cases is too small to serve as the basis of accurate conclusions, the results are quite suggestive, i. e., 14 per cent of the patients were cured by the closed method of drainage as against 55 per cent cured after the resection of a costal cartilage and open evacuation of the pus. It appears from these figures that closed drainage has no place in the treatment of purulent pericarditis.

Empyema developed in 24 of the 99 patients some time during the course of their illness. Whether the suppurative pleuritis occurred primary to, simultaneous with, or subsequent to, the pyopericardium, the combination was a bad one and proved a distinct handicap to the victim's

chances of recovery. Twice the empyema was not discovered until autopsy. In the remaining 22 cases, the condition was recognized clinically and the pus drained off, with 13 recoveries and 9 deaths (4 of the patients were from the University of Maryland Clinic; 1 recovered and 3 died).

In the 22 cases in which operation was resorted to, the empyema involved the left side 12 times, with 7, or 58.33 per cent, recoveries, and 5, or 41.67 per cent, deaths; the right side 7 times, with 6, or 85.71 per cent cures and 1, or 14.29 per cent, deaths; in 2 cases the disease was bilateral, with no recoveries, and in 1 case with a fatal issue, the affected side was not recorded (table 3). These figures seem to indicate not only that a left-sided empyema is more prone to be followed by suppurative pericarditis but that the combination is much more serious than a right-sided empyema and purulent pericarditis.

Pleurisy with effusion developed in 7 patients; 6 of these patients recovered and 1 died.

Secondary Operative Results.—Operative intervention for pyopericardium has been condemned as unwarranted on the ground that if the patient escapes with his life, he will sooner or later succumb to obliterative pericarditis. In such cases, death is delayed but not stayed, and life is prolonged only for a shorter or longer period at the expense of a crippling invalidism, unless the patient is relieved by cardiolysis, a procedure as yet of too recent development to have established its actual value. Fortunately 39 cases are available in this and our first series which throw considerable light on this phase of the subject. Instead of supporting the commonly accepted opinion that a fatal adhesive pericarditis is an inevitable consequence, these cases supply ample proof to the contrary. In all of these cases, at least one year had elapsed since the pericardiotomy, and in one instance as long as thirty-two years (Porter's) and in another (Lilienthal's) twenty-one years had supervened. Thirty-five of these patients were alive, well and at their usual vocations at the time of the report, with their cardiac boundaries within normal limits. One was still alive, but had adhesive pericarditis, and his death was momentarily expected (Davis). Of the 3 remaining patients, 1 had died three years after the pericardiotomy, but the cause of death was not known (Eiselsberg); 1 had died of an abscess of the brain a year later (Johnson), and 1 of an adhesive pericarditis (Darrach).

Thus only 2, or 5.13 per cent, of these 39 patients had acquired intrapericardial adhesions to such degree as to cause baneful symptoms. In the light of these observations, it appears that the occurrence of mortal adhesive pericarditis is exceptional and not as common as heretofore supposed.

We have little doubt that other cases might have come in this category had the patient lived or had not the adhesions been destroyed either at the time of operation or at that of a secondary intervention. For instance, in case 6 of our first series, it was necessary a few days after the pericardiotomy to insert a finger into the wound. Some pocketed pus and a few loose adhesions were detected, and the adhesions were broken up. Eight years later, the patient was well and did not show any evidence clinically of impaired cardiac action. It is too soon, however, to predict the ultimate result, but from present appearances the child is completely cured. Pool had a similar experience, but his patient died thirteen days after the pericardiotomy. In case 7 of our first series, some firm, dense adhesions were found sealing the heart to the pericardium anteriorly at the operation. This patient had a stormy convalescence. Seven years have now elapsed without clinical evidence of any damage to the heart. Delorme, Sievers, Stoker and Allingham found extensive adhesive pericarditis in their cases at autopsy, but none of the patients had survived operation as long as a month.

Drainage.—More than half of the operators showed a preference for tube drainage. Usually two tubes were employed, in which case one was placed in the culdesac on each side of the heart. Next in popularity came rubber tissue. In 1 case the wound was left open, and no artificial drainage was used. The pericardium was sutured to the skin or to the subcutaneous tissues and a tube or gauze put down to but not into the pericardial sac on 9 occasions. When the pericardium was stitched to the muscles or to the skin, a slightly longer time elapsed before complete closure of the wound than in those cases in which the pericardium was treated otherwise. On the whole, there is not much choice between the methods practiced. All are attended by about the same percentage of primary recoveries.

Lindner, Lane and Lilienthal had to discontinue tube drainage, however, because the tube impinged on the heart and by irritating it caused a stormy and irregular cardiac action. Riedel and Eichel, in pericardiotomies performed for conditions other than purulent pericarditis, noticed the same phenomenon.

In Underhill's case, a sharp hemorrhage occurred from the drainage tube two days after the pericardiotomy. This was repeated at intervals until the death of the patient.

Irrigation.—Irrigation was used in 37 cases. Twenty of the patients recovered, 16 died, and in 1 case the result was not mentioned. The solutions used were: acriflavine, an acid solution of hypochlorite (eusol), surgical solution of chlorinated soda, physiologic solution of sodium chloride, hydrogen dioxide, mercurochrome, a flavine dye and quinanil. In 59 instances, no mention was made of irrigation; of the patients, 26

recovered and 30 died. The results in 3 cases were not recorded. In 3 cases it is specifically stated that irrigation was not employed; all of the patients recovered.

It appears from these figures that in most instances irrigation had but a slight influence on the result. We feel that the question of whether to irrigate or not to irrigate depends largely on the character and on the amount of the exudate and on the condition of the patient. We have found this a good rule to follow: If the patient is doing well, leave him alone.

If irrigation is employed, provision must be made, without fail, for the return flow of the irrigating fluid. This means the insertion of two tubes into the pericardial sac. Parker's experience illustrates well the penalty for failure to realize the importance of this precaution. In his case, the pus did not flow well after the pericardiotomy. It was thick and contained membranous shreds. Irrigation was practiced, but the opening in the pericardium became plugged with lymph, and the pressure of the trapped fluid on the heart proved fatal. Rhodes had a similar experience. While he was washing out the pericardium, the catheter became plugged. The patient grew cyanotic, gave a few convulsive jerks and apparently was dead. The catheter was pulled out. This was followed by a gush of irrigating fluid. Respirations began immediately and the patient appeared to be as well as ever, but he died several days later. In Brown's cases, also, the irrigating fluid was trapped, with the occurrence of "Herzdrück," which was promptly relieved on the escape of the fluid.

Among others, Brown, Bransfield, Sherwood and White used surgical solution of chlorinated soda with satisfaction. Its use by Cutter resulted in a marked arrhythmia. This irregularity was preceded by a distinct acceleration of the heart beat. Loucks had to discontinue its use because a bronchial fistula developed. Jopson used it with great trepidation and in fact had to discontinue its use because it was not tolerated.

Prognosis.—The prognosis, though always grave, is by no means hopeless. Even in apparently moribund patients, striking cures have occurred. In this series 18 patients were so listed, with 10 recoveries and 8 deaths. Of much significance from a prognostic standpoint is the etiologic element. Those cases caused by the introduction of pyogenic organisms directly from without on bullets or on knife blades, in which the disease is, therefore, limited to the pericardial sac, give the best percentage of recoveries. The pneumococcic variety yields in round numbers 50 per cent of the cures. The streptococcic and staphylococcic types have the least favorable prognosis.

When the pericarditis is an expression of a generalized septic process, the field for successful operative intervention seems to be small. Yet, limited as it is, it affords the sole chance of averting a fatal issue. On the other hand, practically all patients not operated on or treated only by aspiration die.

Complications necessarily fatal in themselves, unless detected early and promptly remedied, render the prognosis less favorable. Preemi-

TABLE 3.—*Pleural Complications: Empyema*

Case	Side	Operated On	Discovered at Autopsy	Recovered	Died	Comment
5	Left	Yes	....	....	Yes	
12	Left	Yes	....	Yes	....	Closed drainage
17	Left	Yes	....	....	Yes	Closed drainage
22	Left	Yes	....	Yes	....	Right-side fluid aspirated
23	Right	Yes	....	Yes	....	Aspirated
25	Left	Yes	....	Yes	....	
40	Right	Yes	....	Yes	....	
42	Bilateral	Yes	....	....	Yes	Closed drainage
43	Bilateral	Yes	....	....	Yes	Hemorrhage into pleural cavity
46	Right	....	Yes	....	Yes	
47	Left	Yes	....	....	Yes	
55	Left	Yes	....	Yes	....	
59	Left	Yes	....	....	Yes	
68	Right	Yes	....	Yes	....	
71	Left	Yes	....	Yes	....	
72	Right	Yes	....	Yes	....	
77	Right	Yes	....	Yes	....	Two aspirations
79	Left	Yes	....	....	Yes	
82	Right	Yes	....	Yes	....	
84	Left	Yes	....	Yes	....	
85	.....	Yes	....	....	Yes	Entered with empyema
88	.....	....	Yes	....	Yes	Pyopneumothorax
89	Right	Yes	....	....	Yes	
97	Left	Yes	....	Yes	....	
24	.....	22	2	13	11	
		Pleurisy Tapped, Times				
2	.....	....	....	Yes	....	
3	Left	....	....	Yes	....	
20	Right	4	....	Yes	....	
35	Left	....	....	....	Yes	Of a secondary hemorrhage from internal mammary vein
58	.....	....	....	Yes	....	
65	.....	2	....	Yes	....	
67	.....	....	....	Yes	....	
7	.....	2	....	6	1	

nent among these is empyema. It was listed as having occurred 24 times. Twenty-two of the patients with empyema had the pus evacuated by thoracotomy, with 13 recoveries and 9 deaths. In 2 instances, the empyema was discovered at autopsy.

Occasionally, it has been found necessary to reopen the wound and to introduce the finger into the pericardial sac for the relief of secondary pockets of pus. While the mortality is high, cure has been effected even under such unfavorable circumstances.

In the general run of cases, the recovery rate is 51.58 per cent, or 1 of every 2 patients operated on. Much improvement in these results could be hoped for; but, when contrasted with the total collapse of other lines of treatment, these figures are a sufficient argument in favor of pericardiotomy for purulent pericarditis.

SUMMARY AND CONCLUSIONS

In closing we wish to stress the following points:

1. Purulent pericarditis is an abscess and, like a collection of pus anywhere else, should be treated by incision and adequate drainage.

2. Too much cannot be said in favor of early operation, but it should be remembered that late operation does not rob the patient of the hope of cure.

3. Operative treatment should yield a cure in 50 per cent of the cases.

4. The best approach is the costoxiphoid route with resection of the left seventh, sixth and fifth costal cartilages together with a portion of the sternum, when more room is needed.

5. Therapeutic aspiration may be used, on occasion, with profit, but it has no curative value.

6. There are three chief factors that govern prognosis: (1) the time of the operation; (2) the type of the organism, and (3) the original condition of which the pyopericardium is a complication.

7. Purulent foci elsewhere, unless detected early and promptly remedied, render the prognosis less favorable.

8. In the past seven years, there has been no appreciable improvement in the operative mortality rate.

9. Pyopericardium is a disease of youth. Eighty-three per cent of the patients are under 30 years of age.

10. Seventy per cent of the patients have been males, and 30 per cent have been females.

11. Troublesome postoperative adhesive pericarditis does not occur as often as it is generally supposed to do.

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EFFECT OF CARBON ARC RADIATION ON HEALING OF BONE

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The remarkable advances made during the past decade demonstrating the rôle of ultraviolet energy in metabolism, the activation of inert substances and the relationship between ultraviolet rays and vitamin D have fired the enthusiasm of the public and furnished a fertile field for the researches of today and tomorrow. As in the case of many other scientific discoveries, however, commercialism and quackery, by incessantly instructing the laity that radiation, either by way of artificial sources or by the consumption of irradiated products, will cure all ills, have built up a false conception of its real value. To be unduly optimistic concerning the value of radiant energy in the treatment of disease, employing it to the exclusion of a hygienic-dietary régime, and to regard light as a *therapia magna,* are bound to bring discouragement.[1] Sunlight or artificial radiant energy will not cure, it is not a specific form of treatment, and it should not be used without medical guidance and adequate equipment. Further, although radiation may give marked effects in cases of abnormal condition, it plays only a minor part in the daily life of normal persons, who can get along with little or no sunlight provided the diet is adequate.[2]

However, notwithstanding these intimated exaggerations, radiation and irradiated materials have, in the proper hands, brought about some phenomenal results. Among the more outstanding are the effects on serum calcium and inorganic phosphorus in the healing of rickets and osteomalacia. Following these outstanding effects on abnormal mineral metabolism, it was logical to study the problem of fractures. Here there are two wholly contrasting views of the value of the results obtained. On the one hand, one reads: "From what has already been

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1. Mayer, E.: Fundamental and Clinical Aspects of Light Treatment, J. A. M. A. **89**:361 (July 30) 1927.

2. Laurens, H.: Some of the Physiological Effects of Radiant Energy, J. Optic Soc. America **18**:237, 1929.

said about the effects of radiation on phosphorus and calcium metabolism, it might be expected that ultraviolet radiation would be of benefit in cases of ununited fractures, and this is amply borne out by clinical experience. As soon as it has been decided that there is delayed union, radiation should be given, as in this way not only are the reparative processes stimulated and the union of the fragments hastened, but there is a better functional result";[3] or, "there is no correlation between calcium and phosphorus determinations and fractures";[4] again, "ultraviolet radiation does not influence the union of fractures."[5] These and other statements illustrating differences of opinion in this matter stimulated us to carry out a fully controlled study of the subject by experimentally fracturing the fibulas of animals and then administering measured amounts of carbon arc radiation.

REVIEW OF THE LITERATURE

The vast amount that has been written on the effects of solar radiation, artificial radiation and irradiated materials fed by mouth precludes a systematic survey of it in this article. For this, one is referred to the reviews which have appeared, such as those of Clark,[6] Mayer,[7] Rollier[8] and Laurens.[9] In this article reference will be made only to facts pertinent to our own study.

Although it is repeatedly stated that light causes an increase in metabolism, this is not supported by experimental data, and there is adequate proof that higher mammals and man are able to endure long periods of darkness with no evident harmful effects, although metabolism may be somewhat lower in darkness than in light.[2]

Recent studies of rickets have given much evidence as to the action of sunlight, artificial radiation and irradiated materials in the metabolism of calcium and phosphorus. Raczynski,[10] in 1912, first showed the influence of sunlight on these constituents. Two puppies of the

3. Aitken, R.: Ultra-Violet Radiations and Their Uses, Edinburgh, Oliver & Boyd, 1930, p. 1.

4. Murray, C. R.: Repair of Fractures, Minnesota Med. **13**:137, 1930.

5. Coulter, J. S., and Smith, E. M.: Clinical Application of Ultraviolet Rays, Radiology **16**:737, 1931.

6. Clark, J. H.: Physiological Action of Light, Physiol. Rev. **2**:277, 1922.

7. Mayer, E.: Sunlight and Artificial Light Therapy in Tuberculosis, Am. Rev. Tuberc. **5**:75, 1921.

8. Rollier, A.: Social Importance of Heliotherapy in Surgical Tuberculosis, Am. Rev. Tuberc. **15**:521, 1927.

9. Laurens, H.: (*a*) The Physiological Effects of Radiation, Physiol. Rev. **8**:1, 1928; (*b*) The Physiological Effects of Radiant Energy, New York, The Chemical Catalog Company, Inc., 1933.

10. Raczynski, M. J.: Recherches expérimentales sur le manque d'action du soleil comme cause du rachitisme, Compt. rend. Assoc. internat. pédiat. **1**:308, 1912.

same litter were separated, one being kept in the sunlight and the other in darkness. Chemical examination of the bodies revealed that the body of the first puppy contained more calcium and phosphorus than that of the second. Powers and Park [11] definitely demonstrated that sunlight will stimulate a deficient calcium and phosphorus balance. A seasonal tide in the blood phosphates in infants was demonstrated by Hess and Lundagen,[12] and a similar tide in blood calcium in rabbits, by Grant and Gates,[13] the higher levels for calcium in March and December being accompanied by lower levels for phosphorus. Orr, Magee and Henderson [14] definitely demonstrated in pigs the effect of cod liver oil and radiant energy on the assimilation of calcium. When the oil was added to the diet or when the pigs were irradiated, the retention of calcium was raised from a minus quantity to over 60 per cent of the intake. Burton [15] demonstrated an increased retention of calcium and phosphorus in boys who were given a diet high in these minerals and who received ultraviolet radiation. Hess and Lewis [16] pointed out that viosterol increases the calcium and phosphorus not only in patients with rickets or tetany but in normal persons. The results of the complete metabolism studies of patients made by Bauer and Marble [17] present convincing evidence that viosterol increases the amount of calcium absorbed from the gastro-intestinal tract. If this increased absorption occurs at a time when the body needs calcium, there result an increased deposition of calcium and an increased number of trabeculae in the bones.

The numerous studies of the conditions governing the process of ossification have given rise to several theories to account for the phenomena observed. Many observers have used the calcium-phosphorus product as an index of the probable course of the healing process.

11. Powers, G. F., and Park, E. A.: Prevention of Development of Rickets in Rats by Sunlight, J. A. M. A. **78**:159 (Jan. 21) 1922.

12. Hess, A. F., and Lundagen, M. A.: Seasonal Tide of Blood Phosphate in Infants, Proc. Soc. Exper. Biol. & Med. **19**:380, 1922.

13. Grant, J. G. B., and Gates, F. L.: Some Factors Affecting the Levels of the Serum Calcium and Phosphorus of Normal Rabbits, Proc. Soc. Exper. Biol. & Med. **22**:315, 1925.

14. Orr, J. B.; Magee, H. E., and Henderson, J. M.: The Effect of Irradiation with the Carbon Arc on Pigs on a Diet High in Phosphorus and Low in Calcium, J. Physiol. **59**:25, 1924.

15. Burton, H. B.: Influence of Cereals upon Retention of Calcium and Phosphorus in Children and Adults, J. Biol. Chem. **85**:405, 1930.

16. Hess, A. F., and Lewis, J. M.: Clinical Experience with Irradiated Ergosterol, J. A. M. A. **91**:783 (Sept. 15) 1928.

17. Bauer, W., and Marble, A.: Preliminary Note on Mode of Action of Irradiated Ergosterol, New England J. Med. **201**:809, 1929. Bauer, W.; Marble, A., and Claflin, D.: Studies on the Mode of Action of Irradiated Ergosterol, J. Clin. Investigation **11**:1, 1932.

There is diversity of opinion as to the validity of this product as an index, and there are differences in the figures found and proposed as indicative of union and nonunion. Tisdall and Harris,[18] in 1922, reported from clinical observation that certain definite and important changes in the inorganic metabolism invariably accompany repair of bone, namely, a slight increase in the serum calcium and a marked increase in the inorganic phosphorus. Their experimental work with dogs which had undergone artificial fracture and received radiation or irradiated materials gave no reliable results because of the impossibility of immobilizing the fragments.

Johnson [19] stated that nonunion other than that of mechanical origin can be definitely predicted if the product of the calcium and the inorganic phosphorus of the blood falls below 35 and is probable if it falls below 40. He stated the belief that it is improper to attempt to correct nonunion surgically, as is often done, until the causative factor, a low calcium-phosphorus product, is corrected by diet, cod liver oil or heliotherapy.

Petersen,[20] working on dogs with experimental fractures, fed diets containing adequate and inadequate calcium and phosphorus. When the animals were given a diet that markedly reduced the product and a fracture was made, nonunion invariably resulted. When the animals were again placed on adequate diets, resulting in a rise of the product to normal, healing took place. A product of 30 was found to be the figure of differentiation between union and nonunion. In a clinical study Petersen [21] found that in many cases of ununited fracture there was, as an underlying basis, a constitutional disturbance responsible for the condition, demonstrable as a deficiency in the inorganic bone-forming elements of the blood. Of the two elements, calcium and phosphorus, the latter was usually at a low level and at fault. In this type of case there was usually an abundant callus but no calcification, whereas patients with low serum calcium usually showed little or no callus. Petersen again noted that when the product of the inorganic constituents was below 30 there was no healing; when between 30 and 35 slight healing, and when above 35 active healing. In one case irradiation with ultravolet rays from a quartz mercury vapor lamp was very effective.

18. Tisdall, F. F., and Harris, R. I.: Calcium and Phosphorus Metabolism in Patients with Fractures, J. A. M. A. **79**:884 (Sept. 9) 1922.

19. Johnson, R. W.: The Healing Process in Fractures, South. M. J. **21**:394, 1928.

20. Petersen, H. A.: Study of Ununited Fractures with Especial Reference to Inorganic Bone-Forming Elements in the Blood Serum, Bull. Johns Hopkins Hosp. **35**:378, 1924.

21. Petersen, H. A.: A Clinical Study of Ununited Fractures with Special Reference to the Inorganic Bone-Forming Elements of the Blood, J. Bone & Joint Surg. **6**:885, 1924.

Ravdin and Jonas,[22] after studying a large group of normally healing and abnormally healing fractures, came to a conclusion similar to that of Petersen. They recognized that the absorption, excretion and utilization were not simple problems, but highly technical, and that the simple feeding of the salt in which the body was deficient was useless in many cases. Henderson, Noble and Sandiford [23] came to the following conclusions: The failure of a fracture to unite may be due to constitutional abnormalities, but while attempts to determine the abnormal constitutional variables should be made as a routine in addition to the use of surgical methods, the successful treatment of the average ununited fracture is in most cases a surgical problem.

Ravdin and Morrison,[24] in 1928, as a result of their observations, doubted that the product of the inorganic ions could be relied on as a prognostic index of the healing of a fracture. In a study of the serum calcium and inorganic phosphorus after fracture in normal, hypercalcemic and hypocalcemic dogs, they were unable to prophesy the rate of ossification from either the calcium-phosphorus product or the negative logarithm of the ionic product. Speed [25] also found the calcium-phosphorus ionic product unreliable for prognostic use in reference to his clinical observations. Estimations made on several hundred consecutive patients with fractures showed a normal range of serum calcium and inorganic phosphorus with products between 36 and 40. The fracture in some of these patients, however, went on to delayed union and nonunion. Throughout the treatment, the serum calcium content remained practically constant, while the inorganic phosphorus content varied, showing a regular sequence of events. Immediately after the fracture the inorganic phosphorus content was low, but within twenty-four hours it increased and remained high for a time, which seemed to vary with the period of disability, after which it returned slowly to normal. Increased muscular activity seemed to hasten its return, while diet had little or no effect. This change in ionic concentration was found to be about the same after other major operative procedures, except that in the major procedures the fall is more rapid. Speed produced experimental fractures in dogs: (*a*) during a period of a low phosphorus and a slightly lowered calcium content of the blood produced by a deficient diet; (*b*) during a period of high blood calcium content

22. Ravdin, I. S., and Jonas, L.: Studies of Calcium and Phosphorus Metabolism in the Fracture of Bones, Ann. Surg. **84**:37, 1926.

23. Henderson, M. S.; Noble, T. P., and Sandiford, K.: Ununited Fractures with Special Reference to the Chemistry of the Blood, J. Bone & Joint Surg. **8**:607, 1926.

24. Ravdin, I. S., and Morrison, M. E.: Ossification After Fractures; An Experimental Study, Arch. Surg. **17**:813 (Nov.) 1928.

25. Speed, K.: Blood Serum Calcium in Relation to the Healing of Fractures, J. Bone & Joint Surg. **13**:58, 1931.

produced by feeding large amounts of calcium lactate, and (*c*) during a period of low blood calcium content produced by parathyroidectomy, which brought about, in time, a high phosphorus content. As a result of this work, Speed stated the belief that determinations of the calcium and inorganic phosphorus content of the serum are valueless from a prognostic standpoint.

Peters,[26] in reviewing the whole topic of calcification, concluded that it cannot be correlated with the level of the serum calcium value. Even if the fraction of the serum calcium which depends on the protein content of the serum and apparently plays no part in calcification is disregarded, the calcium content is no criterion of the process.

Irradiation or the administration of vitamin D (viosterol) has been used by several investigators as a therapeutic measure, with widely varying results, in cases of fracture of the bone. Knoflach[27] treated patients with fracture of the long bones with viosterol and observed an increase in both the amount and the intensity of the callus in those who received the vitamin in contrast with those who did not. The increase began during the third week after fracture and was most prominent in elderly persons (over 55 years) and in children. Bors[28] administered viosterol to rats and rabbits having experimental fractures of the fibulas and reported an increase in both the amount and the calcification of the callus in those receiving the vitamin D product.

Lewis[29] studied the effect of viosterol on healing in seventeen cases of fracture of the long bones in adults. He was unable to observe any hastening of union or formation of callus. The values for calcium and inorganic phosphorus in the serum were not materially raised. Delayed union was present in six of the patients, and these, too, were not benefited. Cuthbertson[30] concluded that only in certain cases of pathologic fracture and abnormal bone metabolism does the addition of vitamin D to the diet appear to be of benefit. Indeed, the clinical after-history of some of his treated patients was that of delayed union.

By feeding viosterol in daily doses of 2 mg. or less, Grauer[31] observed a stimulation of the osteogenetic layer of the periosteum which

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26. Peters, J. P.: Chemistry and Physiology of Calcification, Am. J. Surg. **10**:530, 1930.

27. Knoflach, I. G.: Behandlung der Knochenbrüche mit bestrahltem Ergosterin, Wien. klin. Wchnschr. **4**:739, 1928.

28. Bors, E.: Vigantol und Fracturheilung, Zentralbl. f. Chir. **2**:3266, 1927.

29. Lewis, K. M.: Noneffect of Irradiated Ergosterol in the Treatment of Fracture, Ann. Surg. **92**:415, 1930.

30. Cuthbertson, D. P.: The Disturbance of Metabolism Produced by Bone and Nonbone Injury, with Notes on Certain Abnormal Conditions of Bone, Biochem. J. **24**:1244, 1930.

31. Grauer, R. C.: Effect of Viosterol on Periosteum in Experimental Fractures, Arch. Surg. **25**:1035 (Dec.) 1932.

resulted in a more rapid healing of experimental fractures in guinea-pigs. Greater doses caused retardation of the healing process, and huge doses (approximately 15 mg.) caused symptoms of osteitis fibrosa.

Swart,[32] experimenting on rabbits and rats, was unable to increase the rate of the healing of fractures or the amount of callus formed by administering viosterol by mouth in daily doses of 3 and 1.25 Gm., respectively. Murray [4] stated the belief that fractures always heal unless there is a mechanical bar to the growth of tissue and that healing is accomplished, as in other traumatized tissue, by the growth of granulation tissue derived from the adjacent traumatized soft parts, namely, the adjacent periosteum and endosteum and the alveolar tissue about the vessels in the marrow cavity and elsewhere. The source of calcium for this new-formed bone is dead, autolyzed bone at the site of fracture and not the blood stream. Vascular changes probably induce local changes in hydrogen ion concentration, which may influence the precipitation of calcium salts from solution or colloidal combination. Bone as a source of calcium can experimentally replace both inorganic and organic salts of calcium. Either precipitation or ferment-splitting activity may be responsible for the deposition of calcium, and the latter seems the more probable. Bone and the circulation through the soft parts are of prime importance in the process of calcification or healing of a fracture, and should therefore be prime objects of attention early in the process of bone healing. Oral administration of calcium and phosphorus and similar drugs is ineffective, and if calcium is needed in any person whose general calcium metabolism is normal, it must be supplied locally and not by way of the blood stream. Coulter and Smith [5] reported that in their experiments with the use of ultraviolet radiation as a therapeutic measure in the healing of fractures they observed no notable influence. They were unable to demonstrate any constant deficiency in calcium in cases of fracture with nonunion.

METHODS

Dogs and rats were selected as the experimental animals. In the case of the dogs, a total of twenty-five, the following plan was adopted:

In group A the fibula on one side was fractured, and then, after it had completely healed, the fibula on the other side was broken in as similar a manner as possible. During the healing of the second fracture, the animal was irradiated.

In group B the procedure was reversed; that is, the animal was irradiated while the first fractured fibula was healing and not irradiated after the second fracture was made.

In group C in seven experiments the two fractures were made not in one animal but in two. This was done not by choice but because of the death of an

32. Swart, H. A.: The Effect of Irradiated Ergosterol on the Healing of Experimentally Produced Fractures in Animals, J. Bone & Joint Surg. **12**:360, 1930.

animal or because the second lesion did not duplicate the first. In these seven experiments in which results from different dogs are compared the animals were similar in form and weight.

In group D in two experiments carbon arc radiation was administered in the same amounts per unit of time during the healing of the two fractures. One of these belongs in group C.

In group E in two experiments no irradiation was given during either healing period. One of these belongs in group C.

In the case of the rat, because large numbers could be readily experimented on and followed simultaneously, a group of from seven to ten animals served as controls for two irradiated groups of a series. The fractures in all the animals were identical. Each animal had only one fracture and one period of healing. Carbon arc radiation, varying in type and amount or in both, was administered to two experimental groups of each series. Determinations were made of the percentage of animals in each group in which the fracture was completely healed at various intervals after the fracture.

Selection and Care of Animals.—All twenty-five dogs were healthy young adults of white or light color, with short hair, and varied in size from small to medium. A preexperimental period was allowed for them to become accustomed to their surroundings and to determine the normal levels for calcium and inorganic phosphorus. Their diet consisted of meat scraps and bones obtained daily from the market. They were housed in outside, semiclosed pens, with sufficient space to move around in easily and thus to exercise mildly.

The rats were all healthy albino males from our own colony, between 3 and 5 months of age and weighing between 200 and 300 Gm. at the beginning of the experimentation. They were kept in groups of from seven to ten in large cages, and food (Bal-Ra [32a]) and tap water were allowed ad libitum. Both dogs and rats were frequently weighed.

Determinations of the Calcium and Inorganic Phosphorus Content of the Serum.—Blood was aspirated from the femoral veins of the dogs at varying intervals and analyzed for calcium by the method of Clark and Collip [33] and for inorganic phosphorus by the method of Fiske and Subbarow.[34] The calcium and the inorganic phosphorus content were not determined for the rats.

Experimental Fracturing.—The fibula was fractured in dogs and rats, an aseptic open osteotomy technic similar to that of Lindsay and Howes [35] and Bors [28] being used. The fibula was chosen because it did not necessitate splinting to keep the ends in alinement, since the tibia acts as a support.

The rats were narcotized with ether in a covered jar and carried lightly during the operative procedure. The leg was prepared for operation by clipping and shaving the hair from the lateral surface and applying tincture of iodine. With the sterile portion of the leg protected by a drape, a longitudinal incision was made and carried down to the fascia at the anterior border of the gastrocnemius. When

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32a. Bal-Ra (obtained from the Valentine Company, of Richmond, Va.) contains: moisture, 9.57 per cent; protein, 29.38 per cent; fat, 5.7 per cent; ash, 9.03 per cent, and carbohydrate, 46.32 per cent.

33. Clark, E. P., and Collip, J. B.: Tisdall Method for Determination of Blood Serum Calcium with a Suggested Modification, J. Biol. Chem. **63**:461, 1925.

34. Fiske, C. H., and Subbarow, Y.: Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375, 1925.

35. Lindsay, N. K., and Howes, E. L.: The Breaking Strength of Healing Fractures, J. Bone & Joint Surg. **13**:491, 1931.

the fascia was divided and the soleus retracted, the fibula was exposed to view. The point of a slender probe was placed under the fibula and a cut made on each side with the points of small sharp scissors. In this way a small piece, just short of 1 mm. in length, was removed. In two preliminary series the fibula was fractured by simply transecting it. This, however, proved unsatisfactory as all the fractures healed too rapidly to allow differences in time required for healing to be recognized. The results for these preliminary series are not included in this report.

No ligatures were used, as the procedure was practically bloodless. The fascia and skin were closed with continuous silk sutures. In all cases the animals walked on the fractured leg as soon as they had recovered from the anesthesia.

The procedure for the dogs was similar, being carried out under ether anesthesia given by cone throughout the operation. The muscles and fascia were closed with continuous silk sutures, while the skin was closed with intermittent linen sutures. Although there was usually profuse bleeding from subcutaneous vessels, this was easily controlled by hemostats. The lesions in the dogs were by no means identical, but for each experiment reported they were alike. The type of lesion varied in the different experiments from a deep V to a shallow crescent shape. A pointed bone forceps was used to make the V-shaped lesions and a round-nosed forceps to make the crescent.

The ease with which duplicate lesions of the bone could be made in the rats was in sharp contrast to the condition in the dogs. In the rats the operation described became such a routine that the entire procedure could be carried out with accuracy on an animal in five minutes. In the dogs this situation did not exist. Indeed, even after careful study of the roentgenograms taken immediately after the primary lesion and with the plate before us during the second operation, it proved impossible to make identical or even approximately similar lesions in many cases. This, plus the fact that in several of the well duplicated lesions there was erosion or breaking through of the remaining bone of the shaft, which completely removed all semblance of identity, made it necessary to discard the data for sixteen dogs.

Irradiation.—The source of radiant energy was a carbon arc lamp. Sunshine carbons and therapeutic C carbons of the National Carbon Company were used in different series and cases. The lamp was operated at between 24 and 27 amperes, with a potential drop across the arc of from 50 to 60 volts. Detailed information concerning the determination by radiometry of the intensity of such radiant energy and its spectral distribution has been given by Laurens.[9b] Owing to changes in the reflecting surfaces of the lamp, the total energy emitted by the Sunshine carbons varied between 0.59 gram calorie per square centimeter per minute at 1 meter distance, with a distribution of 4 per cent of ultraviolet, 42 per cent of luminous and 54 per cent of infra-red rays, and 0.417 gram calories, with a distribution of 3.1 per cent of ultraviolet, 27 per cent of luminous and 69.9 per cent of infra-red rays. For the C carbons the energy varied between 0.461 gram calorie with a distribution of 5.5 per cent of ultraviolet, 12.6 per cent of luminous and 81.9 per cent of infra-red rays and 0.441 gram calorie with a distribution of .4 per cent ultraviolet, 9 per cent of luminous and 87 per cent of infra-red rays.

During the periods of irradiation the dogs were tied on their backs on rounded dog boards, with their abdomens directly exposed to the rays from the flaming arc, and blindfolded to protect the eyes. The rats were placed in hardware cloth tubes in which they were free to move about but were unable to vary their distance from the flaming arc. The amount of energy received per square centimeter of irradiated surface was controlled and varied by changes in the distance from the arc as well as by the duration of the exposure.

Roentgenograms.—Roentgenograms served as the criterion of the healing process. The first picture was taken immediately after the operation, to serve as a record and for study before an attempt was made to duplicate the lesion in another fibula or for comparison to determine how accurate a duplication had been made. Successive roentgenograms were made during the healing process at intervals, greater in the early stages than in the later. When the plate revealed a continuous light shadow, similar to that found in the undamaged shaft and of the same width, the fracture was considered completely healed and fully calcified.

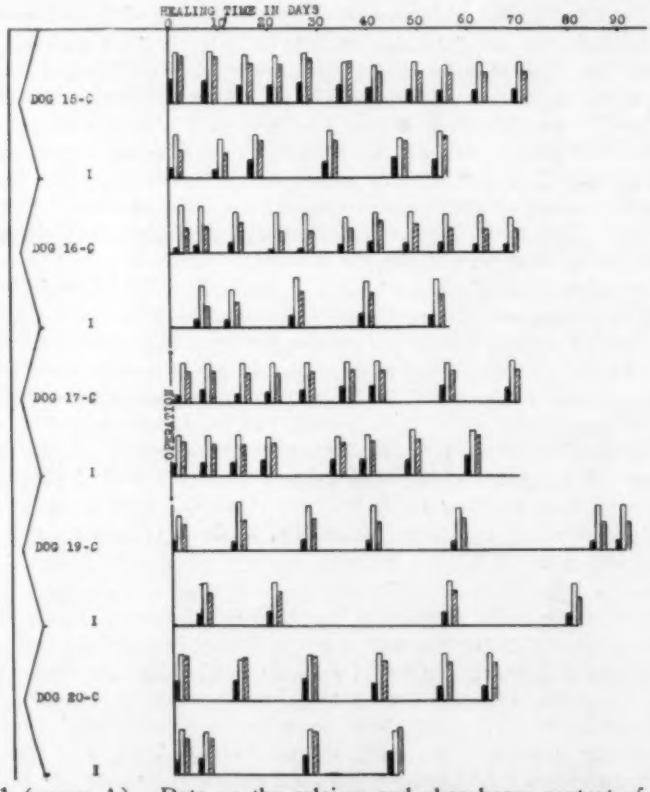

Fig. 1 (group A).—Data on the calcium and phosphorus content of the blood. In figures 1, 3, 4, 6 and 7 the distance between the horizontal black lines represents from 3 to 18 mg. of calcium or of phosphorus per hundred cubic centimeters of blood, or a calcium-phosphorus product of from 0 to 100. The black column indicates the phosphorus content; the white column, the calcium content, and the shaded column, the calcium-phosphorus product. *I* indicates an irradiated animal; *C*, a control animal.

The fact that the callus was not entirely reduced was not considered of significance. Numerous macroscopic examinations of fibulas at autopsy proved that the roentgen criterion was valid.

EXPERIMENTAL RESULTS ON DOGS

Group A.—In this group each of the five animals (dogs 15, 16, 17, 19 and 20) supplied data for a complete experiment. The control period of healing was

carried out first in all cases, while the experimental period of healing (with irradiation) was second. The type, amount and distribution of radiant energy are incorporated in table 1.

The period of healing by irradiation was shorter than the control period of healing in four animals and equal in the fifth (dog 17). These differences ranged from none to 19 days, with an average of 11.6 days. The serum calcium and

TABLE 1.—*Data for the Dogs of Group A*

Dog	Irradiation	Diminished Healing Time, Days	Average Increase During Period of Irradiation, Mg. per 100 Cc.			Radiant Energy Received, Gram Calories per Square Centimeter			
			Serum Calcium	Inorganic Phosphorus	Calcium Phosphorus Product	Total	Distribution		
							Ultraviolet	Luminous	Infra-Red
15	Sunshine carbons, 30 min. daily at 100 cm. for 55 days	+16	—0.4	—0.5	—4.9	781.3	31.3	179.9	570.1
16	Sunshine carbons, 30 min. daily at 100 cm. for 56 days	+13	+0.7	+0.1	+8.0	799.6	31.9	191.9	575.8
17	Sunshine carbons, 30 min. daily at 75 cm. for 70 days	+ 0	+0.5	+0.5	+7.9	1849.9	83.2	555.0	1211.7
19	Sunshine carbons, 30 min. daily at 75 cm. for 81 days	+10	+0.1	+0.6	+10.8	840.5	33.6	336.2	470.7
20	Sunshine carbons, 30 min. daily at 75 cm. for 45 days	+19	—0.3	+0.4	0.0	570.1	23.8	233.3	313.0

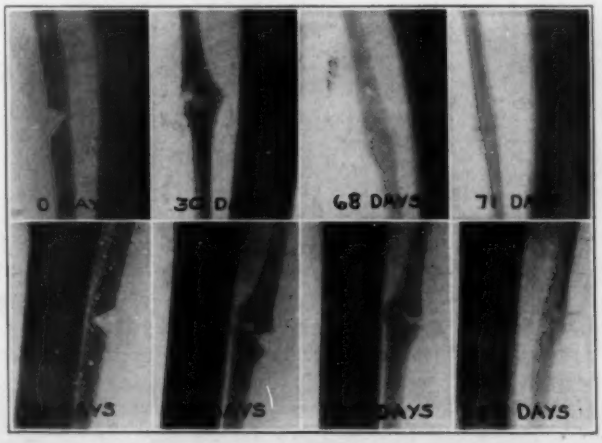

Fig. 2 (group A).—Roentgenograms of the original lesions, two intermediate stages and complete healing of lesions in dog 15. The upper roentgenograms are of the left fibula; the lower ones, the right fibula.

inorganic phosphorus contents remained fairly constant throughout. In three experiments the average serum calcium content was slightly increased during the period of irradiation, while in the other two it was diminished. The average amount of inorganic phosphorus was increased in four and diminished in one of the five experiments. The greatest change that took place in the group in the average content of either calcium or phosphorus was 0.7 mg. per hundred cubic centimeters (table 1). The trends of the calcium, phosphorus and calcium-

phosphorus product were definitely upward during the periods of irradiation in all the experiments, while the opposite trend, or no change, characterized the control determinations (fig. 1).

The total amounts of carbon arc radiation received by each animal during the periods of healing ranged from 1,850 to 570 gram calories per square centimenter, with an average of 968.2 and an average distribution of 4.1 per cent ultraviolet, 31.6 per cent of luminous and 64.3 per cent of infra-red rays. Sunshine carbons were used for all the animals in this series.

The roentgenograms show marked differences in the lesions in the different dogs, but for each dog the two fractures were very similar. In dog 17 the two fractures were almost alike at the beginning, but unfortunately both broke through entirely and in a dissimilar manner. In addition, owing to tension on the leg while the second roentgenogram was being made, the broken ends were drawn farther apart than in the case of the first fracture. The roentgenograms in figure 2 show the original lesions, two intermediate stages and completed healing in the fibulas of dog 15.

TABLE 2.—*Data for Dogs of Group B*

Dog	Irradiation	Diminished Healing Time, Days	Average Increase During Period of Irradiation, Mg. per 100 Cc.			Radiant Energy Received, Gram Calories per Square Centimeter			
			Serum Calcium	Inorganic Phosphorus	Calcium Phosphorus Product	Total	Distribution		
							Ultraviolet	Luminous	Infra-Red
1	C carbons, 30 min. daily at 75 cm. for 31 days	+36	+1.06	+1.2	+16.7	1247.1	46.3	168.8	1032.0
2	C carbons, 30 min. daily at 75 cm. for 31 days	+49	0.0	+0.7	+9.2	1247.1	46.3	168.8	1032.0
5	C carbons, 20 min. three times a week at 75 cm. for 49 days	—20	+0.8	—0.2	+1.9	381.8	17.9	39.3	324.6
18	Sunshine carbons, 30 min. daily at 75 cm. for 120 days	—20	+0.3	+0.6	+8.6	3028.0	121.1	999.7	1907.2
21	Sunshine carbons, 20 min. daily at 100 cm. for 35 days	+ 8	+0.7	+1.0	+17.2	525.5	21.0	126.1	378.4

Group B.—In this group each of the five animals (dogs 1, 2, 5, 18 and 21) supplied data for a complete experiment. The procedure was the reverse of that used for group A; that is, the period of healing by irradiation was first, and the control period of healing was second. The type, amount and distribution of radiant energy are given in table 2.

The period of healing with irradiation was shorter than the control period of healing in three of the five experiments of this group and longer in two. The difference ranged from 49 days more to 20 days less, with an average of 10.6 days more (table 2). The average changes in the calcium and inorganic phosphorus content of the serum were slight, the greatest being 1.2 mg. The average value for serum calcium increased in four animals during the period of healing by irradiation and was unchanged in the fifth. The average value for inorganic phosphorus increased in four animals and decreased in one (table 2). The calcium-phosphorus product was noticeably higher during the period of irradiation in all cases (fig. 3).

The total amount of radiant energy given to these animals during the first period of healing varied from 3,028 to 381.8 gram calories, with an average of

1,285.9 and an average distribution of 4 per cent of ultraviolet, 19 per cent of luminous and 77 per cent of infra-red rays. Therapeutic C carbons were used for irradiating dogs 1, 2 and 5, and Sunshine carbons for dogs 18 and 21 (table 2 and fig. 3).

The roentgenograms showed that the fractures in the different dogs varied considerably, although they were quite similar in the two fibulas of the individual animals.

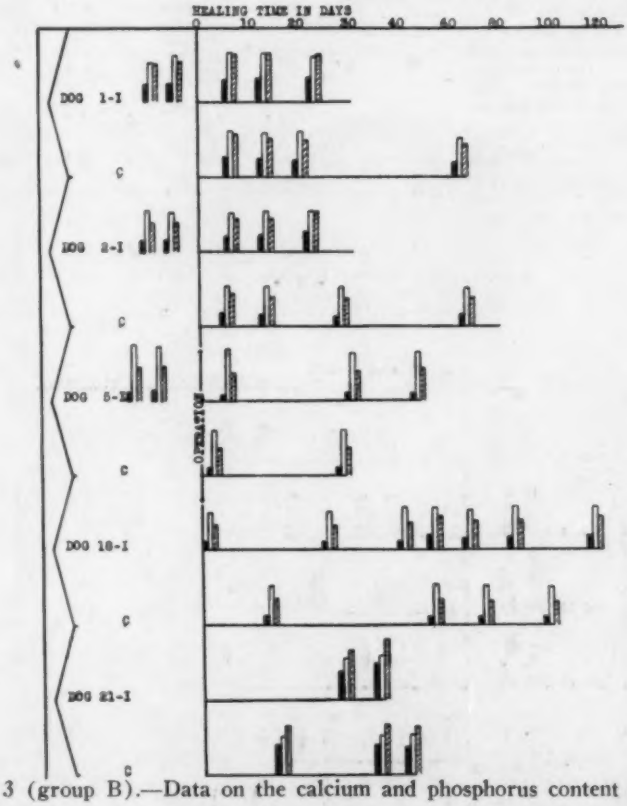

Fig. 3 (group B).—Data on the calcium and phosphorus content of the blood.

Group C.—In this group, five pairs (dogs 5 and 4, 13 and 14, 22 and 23, 24 and 25, and 8 and 7) supplied the data. The pairs were selected on the basis of similarity in body build and weight. One of each pair was irradiated during the period of healing of the fracture, while the other was not and served as the control. The type, amount and distribution of radiant energy are given in table 3.

The healing time for the irradiated dog was shorter than that for the control in three of the five pairs of dogs and longer in two pairs. The differences ranged from 19 days more to 24 days less, with an average of 3 days more. The average calcium and inorganic phosphorus contents of the serum of the irradiated animals varied only slightly from that of the controls in the same experiment. The variations were of somewhat greater magnitude than in groups A and B, owing, in part at least, to different basal levels of the animals. (Note the preoperative levels of dogs 13 and 14 [fig. 4].) The trend of the calcium-phosphorus product decreased in only one of the irradiated dogs as compared with its control (pairs

TABLE 3.—*Data for the Dogs of Group C*

Dog	Irradiation	Diminished Healing Time, Days	Average Increase During Period of Irradiation, Mg. per 100 Cc.			Radiant Energy Received, Gram Calories per Square Centimeter			
			Serum Calcium	Inorganic Phosphorus	Calcium Phosphorus Product	Total	Distribution		
							Ultraviolet	Luminous	Infra-Red
3	C carbons, 20 min. every second day at 75 cm. for 41 days	— 5	0.0	—1.3	—13.0	577.0	30.0	68.0	479.0
13	C carbons, 20 min. every second day at 75 cm. for 28 days	+19	+0.4	+2.1	+26.0	145.6	7.3	17.5	120.8
22	Sunshine carbons, 30 min. daily at 100 cm. for 35 days	+14	+0.6	+0.2	+2.6	511.2	20.4	117.6	373.2
24	Sunshine carbons, 30 min. daily at 75 cm. for 41 days	+11	—0.7	+1.3	+3.8	1064.0	42.6	297.9	723.5
8	C carbons, 20 min. three times a week at 75 cm. for 11 weeks	—24	+0.7	+0.2	+7.3	546.2	23.5	60.1	462.6

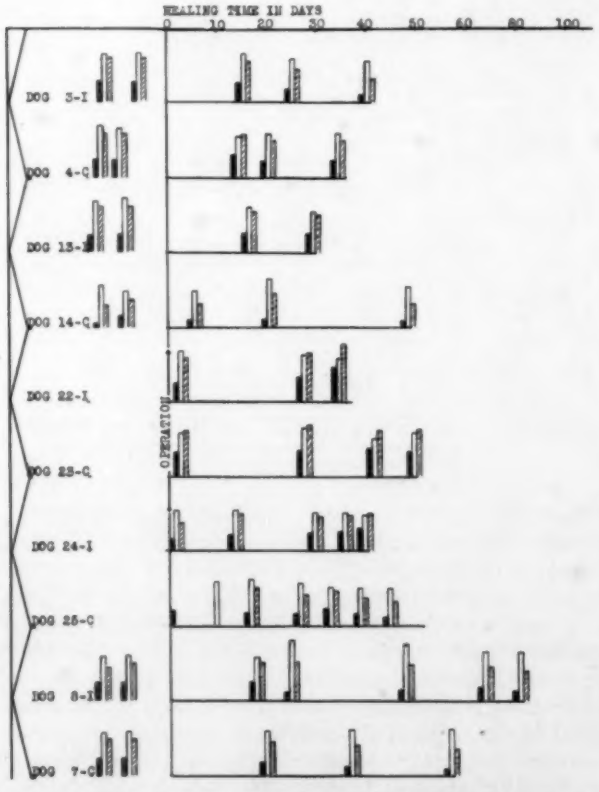

Fig. 4 (group C).—Data on the calcium and phosphorus content of the blood.

3 and 4), and the fracture in the control (dog 4) healed in a slightly shorter time than did that in the irradiated dog (dog 3 [table 3]).

The total amount of radiant energy given to the irradiated animals of this group varied from 1,064 to 145.6 gram calories, with an average of 568.8 and an average distribution of 4.5 per cent of ultraviolet, 17 per cent of luminous and 78.5 per cent of infra-red rays.

Group D.—This group consisted of three animals (dogs 6, 8 and 9). In dog 6 both fibulas were fractured, the second after the healing of the first; they were allowed to heal successively, the animal being irradiated in each case. Dogs 8 and 9 had similar lesions and were thus comparable. Both dogs were irradiated during the healing of their fractures.

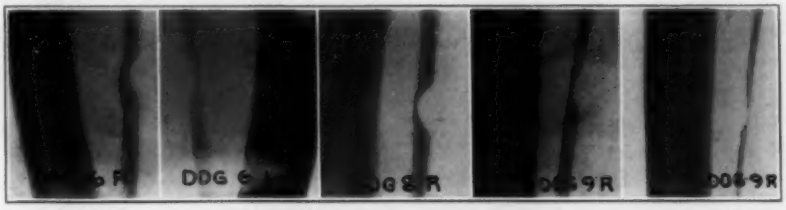

Fig. 5 (group D).—Roentgenograms of the original lesions of the dogs in this group. The second roentgenogram of dog 9 shows the lesion 167 days after operation.

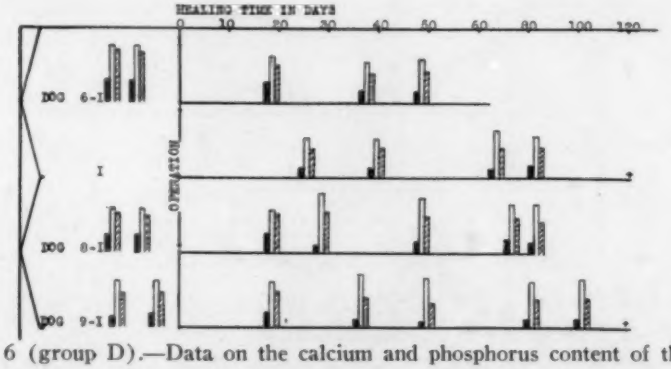

Fig. 6 (group D).—Data on the calcium and phosphorus content of the blood.

The first fracture in dog 6 healed in 64 days, while the second was still not entirely healed in 120 days, thus showing a difference of at least 56 days. The calcium and inorganic phosphorus contents of the serum varied only slightly; enough, however, to make the determinations in the first period of healing show a detectable higher average calcium-phosphorus product (fig. 5).

The healing times were also very different in dogs 8 and 9. The fractures were almost identical (fig. 5), and the body builds of the two animals were very similar. The fracture in dog 8 healed in 81 days; in dog 9 there were still no signs of healing in 167 days after the production of the fracture, thus illustrating true nonunion (fig. 6, table 4).

Group E.—The three animals (dogs 12, 10 and 11) in this group were not irradiated. Both fibulas of dog 12 were fractured and allowed to heal successively, as in dog 6, group D. Dogs 10 and 11 had similar lesions and were thus comparable.

TABLE 4.—*Data for the Dogs of Group D*

Dog	Irradiation	Difference in Healing Time, Days	Average Increase During the Shorter Healing Period, Mg. per 100 Cc.			Radiant Energy Received, Gram Calories per Square Centimeter			
			Serum Calcium	Inorganic Phosphorus	Calcium Phosphorus Product	Total	Distribution		
							Ultraviolet	Luminous	Infra-Red
6	C carbons, 20 min. three times a week at 75 cm. through both healing periods	56+	−0.3	+0.2	+3.1	460.9 543.0	22.1 24.4	49.3 54.3	389.5 464.3
8 and 9	C carbons, 20 min. three times a week at 75 cm. for 11 weeks	86+	+0.2	+0.7	+11.3	546.2 546.2	23.5 23.5	60.1 60.1	462.6 462.6

The first fracture in dog 12 healed in 38 days, and the second in 57 days, a difference of 19 days. The serum calcium content was, on an average, 1.1 mg. higher in the longer period of healing, while the inorganic phosphorus was higher by an average of 1.8 mg. in the shorter period of healing. The calcium-phosphorus product was noticeably greater during the shorter period of healing.

In the other experiment of this group there was a difference of 35 days in the healing time. The fibula of dog 10 healed in 35 days, while that of dog 11 took 70 days, or twice as long. The average calcium and inorganic phosphorus contents of the serum were higher in dog 11, and thus the calcium-phosphorus product was also higher in the more slowly healing animal (fig. 7; table 5).

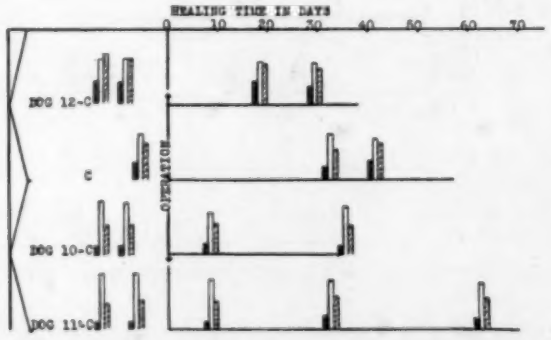

Fig. 7 (group E).—Data on the calcium and phosphorus content of the blood when no irradiation was given during the period of healing.

Summary.—In the three groups (A, B and C) there were fifteen pairs of similar fractures. During the healing period of one fracture of each pair, the animal was irradiated. The healing time of the irradiated in contrast to the control fracture was diminished in ten instances, increased in four and equal in one. The average diminished healing time was 8.5 days.

Taking all five groups together, that is, adding groups D and E and contrasting the healing time of the four fractures of the former with

the four unirradiated fractures of the latter, a much different final figure is found. The average difference is a minus figure, or a diminished average healing time of 5.7 days in the controls. The lesions of the bone in group D are in general decidedly more severe than those in group E (figs. 6 and 8). If we omit the two very abnormal periods of healing, namely, the second period for dog 6, group D, and dog 9, group E, still another difference is obtained. The average period for the seventeen remaining periods of healing by irradiation is 55.8 days, while for the nineteen control periods it is 59.5 days; thus there is a difference of 3.7 days in favor of the periods of treatment with irradiation.

TABLE 5.—*Data for Dogs of Group E*

Dog	Irradiation	Difference in Healing Time, Days	Increase During the Shorter Healing Period		
			Serum Calcium	Inorganic Phosphorus	Calcium-Phosphorus Product
12	None.....	19	—1.1	+1.8	+13.0
10 and 11	None.....	35	—0.2	—0.2	— 6.3

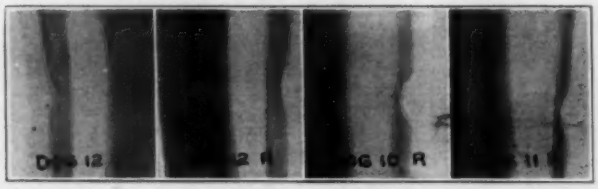

Fig. 8 (group E).—Roentgenograms of the original lesions of the dogs in this group.

The weights, which were taken frequently for all the animals, are not referred to in any of the experiments, for in all cases the curves for weight were well within the range of normal; no correlation was found between the weights and the time of healing.

EXPERIMENTAL RESULTS ON RATS

The experimentation on rats was performed in three series; a total of eighty healthy male rats between the ages of 3 and 5 months and weighing between 200 and 300 Gm. at the beginning of experimentation were used. The animals were weighed frequently, and all showed a normal gain; thus the weights are not reported.

In each of the three series there were three groups of from seven to ten animals each. Group 1 of each series was irradiated with Sunshine carbons, and group 2 with therapeutic C carbons; group 3 served as a control.

The lesions of the bone in all the animals were identical. Pictures of the lesions made in the ten animals of group 1 of series 1 show how similarly the lesions of the bone were made.

In all the groups the experiment was terminated about 70 days after operation was performed. The last roentgenogram taken and one taken about the middle of the experimental period are referred to in the results.

Series I.—There were thirty animals in this series—ten animals in each group. In group 1, however, two animals were accidentally killed a few days after they were operated on; thus only eight are considered in the experiment.

Group 1 received a total of 571.2 gram calories per square centimeter of Sunshine carbon radiation, with an average distribution of 3.2 per cent of ultraviolet,

TABLE 6.—*Experimental Results with Rats*

Series	Group	Irradiation	Days	Fractures Healed, Number	Fractures Unhealed, Number	Fractures Healed, Percentage	Fractures Unhealed, Percentage
I	1	Sunshine carbons, 30 min., three times a week at 75 cm.	30	5	3	62.5	37.5
			60	6	2	75.0	25.0
	2	C carbons, 15 min., three times a week at 75 cm.	30	2	8	20.0	80.0
			60	3	7	30.0	70.0
	3	Controls.....	30	2	8	20.0	80.0
			60	4	6	40.0	60.0
II	1	Sunshine carbons, 20 min. every second day at 75 cm.	31	6	2	75.0	25.0
			67	7	1	87.5	12.5
	2	C carbons, 10 min. every second day at 75 cm.	31	3	4	42.8	57.2
			67	4	3	57.2	42.8
	3	Controls.....	31	2	8	20.0	80.0
			67	5	5	50.0	50.0
III	1	Sunshine carbons, 20 min. every second day at 75 cm.	45	3	4	42.8	57.2
			73	4	3	67.2	42.8
	2	C carbons, 10 min. every second day at 75 cm.	45	0	9	00.0	100.0
			73	0	9	00.0	100.0
	3	Controls.....	45	2	7	22.2	77.8
			73	3	6	33.3	66.7
Totals		Groups 1 (23 animals).....		17	6	73.9	26.1
		Groups 2 (26 animals).....		7	19	26.9	73.1
		Groups 3 (29 animals).....		12	17	41.3	58.7

28.8 per cent of luminous and 68 per cent of infra-red rays, in the 61 days of healing. Group 2 in the same period of time received 308.5 gram calories of therapeutic C carbon radiation with an average distribution of 5.5 per cent of ultraviolet, 11.0 per cent of luminous and 83.5 per cent of infra-red rays (table 6).

After 30 days of healing, the roentgenograms showed that five, or 62.5 per cent, of the fractures in group 1 were healed; two, or 20 per cent, in group 2, and two, or 20 per cent, in the control group. After 60 days of healing, six, or 75 per cent, of the fractures in group 1 were healed; three, or 30 per cent, in group 2, and four, or 40 per cent, in group 3 (figs. 9, 10 and 11; table 6).

Series II.—In this series there were twenty-five animals—eight in group 1, seven in group 2 and ten in group 3.

Group 1 received a total of 510 gram calories of Sunshine carbon radiation with an average distribution of 3.9 per cent of ultraviolet, 33.8 per cent of luminous and 62.3 per cent of infra-red rays during the 67 days. Group 2 received a total of 268 gram calories of therapeutic C carbon radiation with an average distribution of 5.5 per cent of ultraviolet, 12.5 per cent of luminous and 82 per cent of infra-red rays during the period of healing.

At the end of 31 days of healing, the roentgenograms showed that six, or 75 per cent, of the fractures in group 1 were healed; three, or 42.8 per cent, in

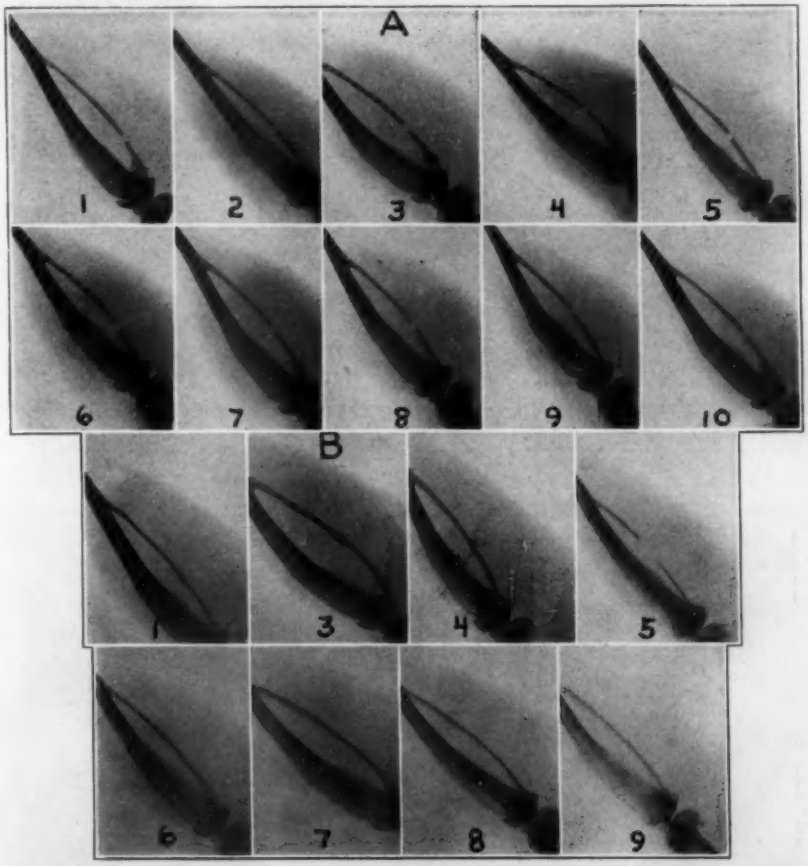

Fig. 9 (series I, group 1).—*A*, roentgenograms of the original lesions of the rats in this group, and *B*, roentgenograms of the lesions 60 days after operation.

group 2, and two, or 20 per cent, in group 3. At the termination of the series, after 67 days of healing, seven, or 87.5 per cent, of the fractures in group 1 were healed; four, or 57.2 per cent, in group 2, and five, or 50 per cent, in group 3 (table 6).

Series III.—This series was composed of twenty-five animals; seven in group 1, nine in group 2 and nine in group 3.

During the period of healing group 1 received a total of 550.4 gram calories of Sunshine carbon radiation with an average distribution of 3.6 per cent of ultra-

violet, 32.2 per cent of luminous and 64.2 per cent of infra-red rays. Group 2 received a total of 289.6 gram calories of therapeutic C carbon radiation with an average distribution of 5 per cent of ultraviolet, 11.5 per cent of luminous and 83.5 per cent of infra-red rays during the 73 days.

Roentgenograms taken on the forty-fifth day of the healing period showed that three, or 42.8 per cent, of the fractures in group 1 were healed; none in group 2,

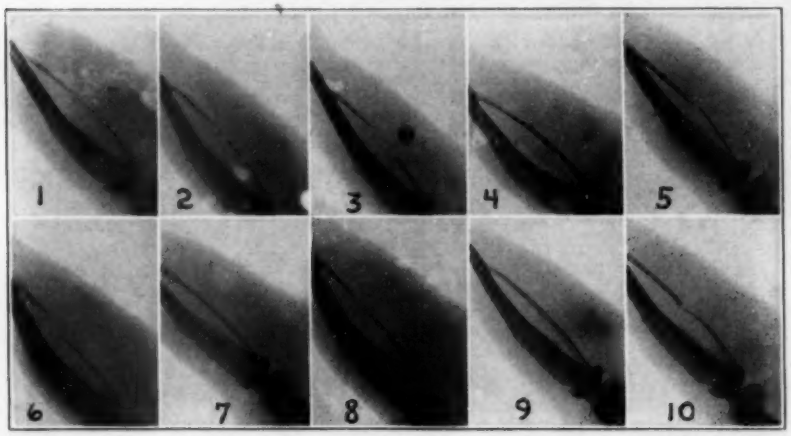

Fig. 10 (series I, group 2).—Roentgenograms of the fibulas of rats 60 days after operation.

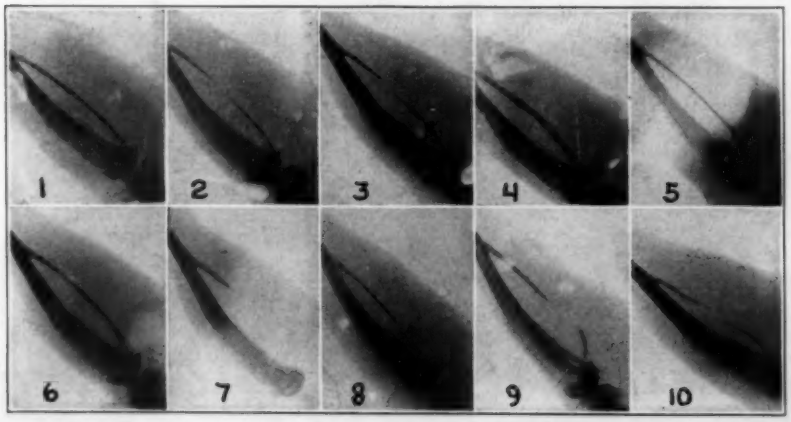

Fig. 11 (series I, group 3).—Roentgenograms of the fibulas of the rats 60 days after operation.

and two, or 22.2 per cent, in group 3. On the 73d day of healing, after which the series was terminated, four, or 57.2 per cent, of the fractures in group 1 were healed; none in group 2, and three, or 33.3 per cent, in group 3.

Summary.—Considering all the groups of the same kind together, irrespective of series, a more representative percentage figure is obtained.

This can well be done, for the only factor of difference is a small difference in the sum total of the same type of radiant energy received.

In group 1, composed of twenty-three animals that received Sunshine carbon radiation, seventeen, or 73.9 per cent, of the fractures healed at the time of terminating the respective series; in group 2, composed of twenty-six animals that received C carbon radiation, seven, or 26.9 per cent, of the fractures healed, and group 3, composed of twenty-nine nonirradiated animals, twelve, or 41.3 per cent of the fractures healed in the same length of time (table 6). It is thus evident that in rats Sunshine carbon irradiation hastened healing and that therapeutic C carbon irradiation had no effect or retarded the process of healing.

COMMENT

The procedures in groups A and B of the dogs were reversed to test whether the length of time of experimentation was correlated with the rapidity of the healing process. It might be expected that the longer an animal is kept under experimental conditions, the less active is the ability of the bone to regenerate. That this is not true is borne out by considering the results obtained with the dogs in which the fracture went through two processes of healing, namely, groups A and B, dog 6 of group D and dog 12 of group E. Four fibulas in group A (dogs 15, 16, 19 and 20) and two in group B (dogs 5 and 18), a total of six, or 50 per cent, of the twelve considered, healed more rapidly following the second fracture. One fibula, or 8.35 per cent (dog 17), healed in the same length of time, and five, or 41.65 per cent (dogs 1, 2 and 21 of group B, dog 6 of group D and dog 12 of group E), took longer to heal following the second fracture. The nutritional state, as judged from weights and general appearance, was normal for all these animals during the experimentation.

The material of group C, in which two dogs were paired in each experiment, was not planned for, but as it accumulated it was analyzed in order to utilize data on animals in which the two fractures in the same animal did not approach similarity but in which one was much like a fracture in another animal of approximately the same weight and type. Later in the work, however, animals were paired in this way intentionally. It is evident that this group was not so well controlled as were groups A and B, in which each animal served as its own earlier or later control. This, however, is the type of data that must be considered clinically, and thus, from that point of view, may be more valuable than that from the more accurately controlled groups.

Groups D and E were designed to show the amount of variation in healing time which could be expected when the experimental conditions were absolutely similar, namely, when the animals in group D

were irradiated and when those in group E were not irradiated. Unfortunately, the groups were not sufficiently large to justify any far reaching conclusions.

There is no apparent correlation between the calcium-phosphorus product and the rate of healing of a fracture and ossification. This finding, therefore, substantiates the conclusions of Ravdin and Morrison [24] and Speed [25] from work on dogs, namely, that the calcium-phosphorus product cannot be relied on as a prognostic index of the rate of regeneration of bone. In group A, in which the period of healing by irradiation was shorter than the control period in four experiments and the same in the fifth (dog 15, one of the outstanding examples of diminished healing time with irradiation), there was a lower average content of calcium and of inorganic phosphorus in serum, and thus there was a lower calcium-phosphorus product, during the shorter period of healing by irradiation. Dog 19, of the same group, showed equal average calcium-phosphorus products for the two periods of healing, and yet the period of healing was 10 days less for the irradiated fracture (table 1). In group B all the animals showed higher average calcium-phosphorus products during the periods of healing by irradiation, although in two animals (dogs 5 and 18) the fracture healed more rapidly during the control period (table 2).

In the one true instance of nonhealing (dog 9), the amount of calcium and of phosphorus and the calcium-phosphorus product were always well within the range of normal. Indeed, in only one set of determinations did the calcium-phosphorus product fall below 50. This is contrary to the results obtained by Johnson [19] and Petersen,[21] who found that nonunion occurred only in cases in which the calcium-phosphorus product was below 35. On the other hand, it is in accord with the point of view more generally held, namely, that there is no correlation between the calcium-phosphorus product and the rate of healing of the fracture.

We may be criticized for dogmatic statements concerning the exact healing time because the roentgenograms taken near the end of a period of healing were sometimes 10 days apart, so that the exact day on which healing was complete cannot be given more closely than that. However, essentially the same procedure was followed in determining the date of healing of both fractures of an experiment, and thus no unfair advantage can be claimed for either the irradiated or the nonirradiated (control) fracture.

It is questionable whether the accelerated healing produced by irradiation, observed when the irradiated fibulas are contrasted with the controls (8.5 days in groups A, B and C and 3.7 days when groups D and E, less the second period of healing for dog 6 and the period of healing for dog 9, are added), is of either scientific or practical sig-

nificance. However, as Murray [36] said: "The treatment of fractures is today an economic problem. End results are to be estimated in dollars and cents." Thus, the time taken to secure the end-results is of considerable importance, and, as Murray suggested, a diminished period of healing of the order of magnitude here observed may be of practical significance at least.

It must be remembered that the work was done on presumably normal animals with normal bone-regenerating ability. If the work had been carried out on abnormal animals, all other factors remaining constant, the results might have been a great deal different.

The markedly different results obtained in the work with rats with the Sunshine carbon radiation as contrasted with the therapeutic C carbon radiation is of some interest. In every series the total amount of Sunshine carbon irradiation given to group 1 was greater than the amount of therapeutic C carbon radiation given to group 2. When the results in each case were compared with those obtained in the controls, the Sunshine carbon irradiation appeared to aid the process of healing, while the therapeutic C carbon irradiation seemed to retard it. The C carbons emit a higher percentage of ultraviolet and infra-red rays than do the Sunshine carbons, but in no series did the total amount of these portions of the spectrum excel, or even equal, the amounts given when the animals were irradiated with the Sunshine carbons. Thus it seems evident that there was something about the spectrum emitted by the C carbons, and not the total amounts of the different components received by the animals, that was detrimental. Coblentz, Stair and Hogue [37] have shown that C carbons emit a larger percentage of the short ultraviolet wavelengths, which produce more erythema than do the rays from the Sunshine carbons. This greater concentration of the short erythema-producing ultraviolet wavelengths may lead to a more marked vasodilatation with possibly an increase in the volume flow of blood, as has been demonstrated in some cases in dogs.[38] Jones and Roberts [39] expressed the belief that an increased flow of blood is a detriment to healing of the bone, and McMaster and Roome [40] demon-

36. Murray, C. R.: Proper Place of Physical Therapy in the Treatment of Fractures, J. A. M. A. **97**:235 (July 25) 1931.

37. Coblentz, W. W.; Stair, R., and Hogue, J. M.: Tests of a Balanced Thermocouple and Filter Radiometer as a Standard Ultraviolet Dosage Intensity Meter, Bur. Stand. J. Research **8**:759, 1932.

38. Pollock, B. E.: The Effect of Carbon Arc Radiation on the Cardiac Output in Dogs, Thesis, Tulane University Graduate School, 1933.

39. Jones, R. W., and Roberts, R. E.: Decalcification and Ossification, Brit. J. Surg. **21**:461, 1934.

40. McMaster, P. E., and Roome, M. W.: Effect of Sympathectomy on Bone Repair, Proc. Soc. Exper. Biol. & Med. **30**:123, 1932.

strated on dogs that lumbar sympathectomy, which brings about vasodilatation of the extremity, leads to retardation in the healing of a fracture.

A discussion of the rôle played by the periosteum and endósteum in the healing of fractures is not believed to be pertinent in this presentation, for in all of the fractures contrasted, the lesions of the bone, and thus the periosteum and endosteum, were similar.

SUMMARY

Experimental fractures of the fibula were studied in twenty-five normal dogs and eighty normal rats. All the rats were of similar size and age and sustained like fractures. They were grouped for comparison according to the type and amount of carbon arc radiation received during the period of healing. The fractures in the dogs were paired for comparison only when the two were proved similar or identical by means of roentgenograms: This occurred in the same dog in twelve cases and in two dogs of similar body build and size in seven cases. Measured amounts of carbon arc radiation were given during the period of healing to one fracture of each pair; the other served as a control.

Roentgenograms were taken at intervals to show the progress of healing. For the rats the percentage of fractures healed per group after a certain length of time was ascertained, while for the dogs the total length of the healing process in days was noted. During the periods of healing allowed, 73.9 per cent of the fibulas irradiated with Sunshine carbons, 26.9 per cent of those irradiated with therapeutic C carbons and 41.3 per cent of the controls healed. If two periods of very abnormal healing in the experiments on the dogs are omitted, the average healing time for the fractures was 3.7 days shorter when the animals were irradiated than when they were not.

Determinations of the calcium and the inorganic phosphorus content of the serum were made for the dogs at frequent intervals, but no correlation was demonstrable between them or their product and the length of the periods of healing. The rapidity of the process of healing was not a function of the duration of the experimental conditions of an animal. The weight curves of the animals were all well within the range of normal.

CLINICAL ASPECTS OF STRUMA LYMPHOMATOSA (HASHIMOTO)

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Struma lymphomatosa (Hashimoto) is a rare type of abnormality of the thyroid gland, first described by Hashimoto in 1912.[1] Because of the infrequency of its occurrence, this type of goiter has been discussed almost exclusively by pathologists who, following Hashimoto's work, occasionally have noted in certain cases the curious histology which he described. By clinicians this lymphoid infiltration of the thyroid is generally considered as a type of chronic thyroiditis, usually Riedel's struma, which it closely resembles in many respects.[2] Since, however, pathologists[3] occasionally report this rare condition, it is of importance that the clinical features of struma lymphomatosa be reviewed and the results of treatment noted.

The fundamental picture in struma lymphomatosa is that of a degenerative change in the thyroid gland, unaccompanied by evidence of acute inflammatory process. Microscopically one sees a diffuse lymphoid infiltration between the follicles, with the frequent formation of secondary nodules. These secondary nodules often reach a large size and ordinarily occupy the central third of a focus of lymphocytic infiltration. There tends to be a variation in the intensity of the lymphocytic infiltration in a gland, ranging from only sparse lymphocytes scattered between colloid-containing follicles, or even absence of infiltration in

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1. Hashimoto, H.: Zur Kenntnis der lymphomatösen Veränderung der Schilddrüse (Struma Lymphosatosa), Arch. f. klin. Chir. **97**:219, 1912.

2. Riedel: Die chronische, zur Bildung eisenharter Tumoren führende Entzündung der Schilddrüse, Verhandl. d. deutsch. Gesellsch. f. Chir. **25**:101, 1896.

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certain portions of the gland, to complete obscuring or displacement of the normal architecture by confluent masses of lymphocytes, usually presenting a variable number of secondary nodules.

The cells, which sometimes are contained within the colloid of the follicles, normally monocytes, may be lymphocytes in this condition.

The thyroid follicles present tend to be grouped closely together, in many instances so that one sees what might at first appear to be foci of thyroid tissue in a lymph node. However, the organization of the lymphoid tissue into a definite node does not take place; that is, there is no formation of stroma or of sinuses.

Fig. 1 (case 9).—A photograph of the specimens of thyroid gland removed. Note the density of the gland, the preservation of the normal thyroid contour and the numerous fine fibrous septums.

Rarely a few plasma cells appear in the interstitial tissue.

There is ordinarily no involvement of other structures, although occasionally there may be slight enlargement of regional lymph nodes. Splenic enlargement is never encountered.

At times, a marked lymphocytic infiltration simulating this lesion is presented in patients with long-standing hyperthyroidism, particularly in heavily iodized patients, in whom lymphoid infiltration with secondary follicle formation is by no means unknown.

From the diverse range of lymphocytic infiltrations in the thyroid, struma lymphomatosa can best be differentiated by the absence of evi-

dence of marked thyroid hyperplasia and atrophy of the thyroid substance, often accompanied by the peculiarly glossy, acidophilic epithelial cells sometimes seen in degenerative processes.

Fibrosis is rarely a prominent feature in this condition, in contrast to Riedel's struma. A moderate amount is often present, however. While in Riedel's struma fibrosis extends diffusely into surrounding structures, in this disease fibrosis is always limited by the capsule of the gland.

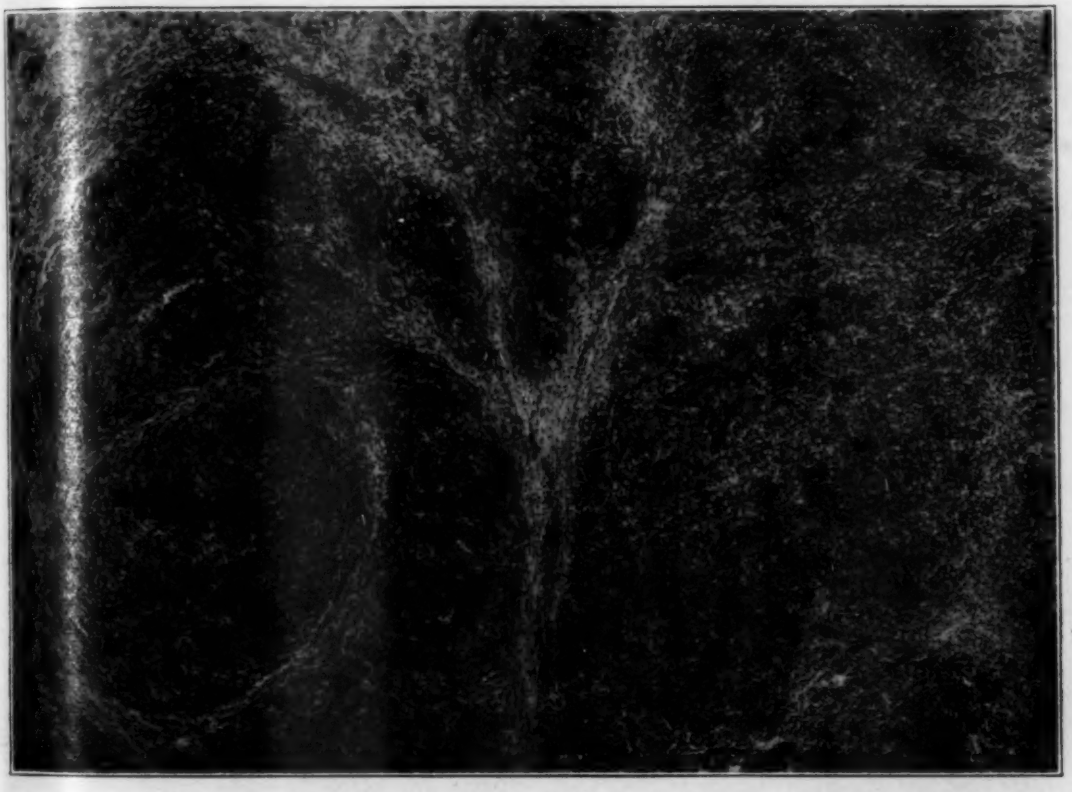

Fig. 2 (case 1).—Photomicrograph (× 50) of a section from the thyroid gland, showing dense lymphoid infiltration and fibrosis and also strands of fibrous tissue. This is an advanced case.

We do not know whether the amount of diffuse fibrosis in the thyroid is related to the duration of the process or not. However, it does seem definitely to be related to the amount of atrophy of the thyroid parenchyma, and as we regard this as secondary to lymphocytic infiltration, the fibrosis is dependent on the degree of lymphocytic infiltration that has taken place.

The suggestion has been made that struma lymphomatosa represents merely one phase in a systemic disease process involving lymphoid

tissue. However, this seems unreasonable in view of the fact that patients suffering from this condition present no generalized disease and the only changes in general constitution are those which can be definitely related to thyroid insufficiency pursuant to the local changes in the glandular tissue or to subtotal thyroidectomy.

Struma lymphomatosa, then, may be regarded pathologically as a lymphocytic infiltration of the thyroid of unknown etiology, inducing an atrophy of the glandular substance and accompanied by a varying degree of interstitial fibrosis. The condition is progressive in the

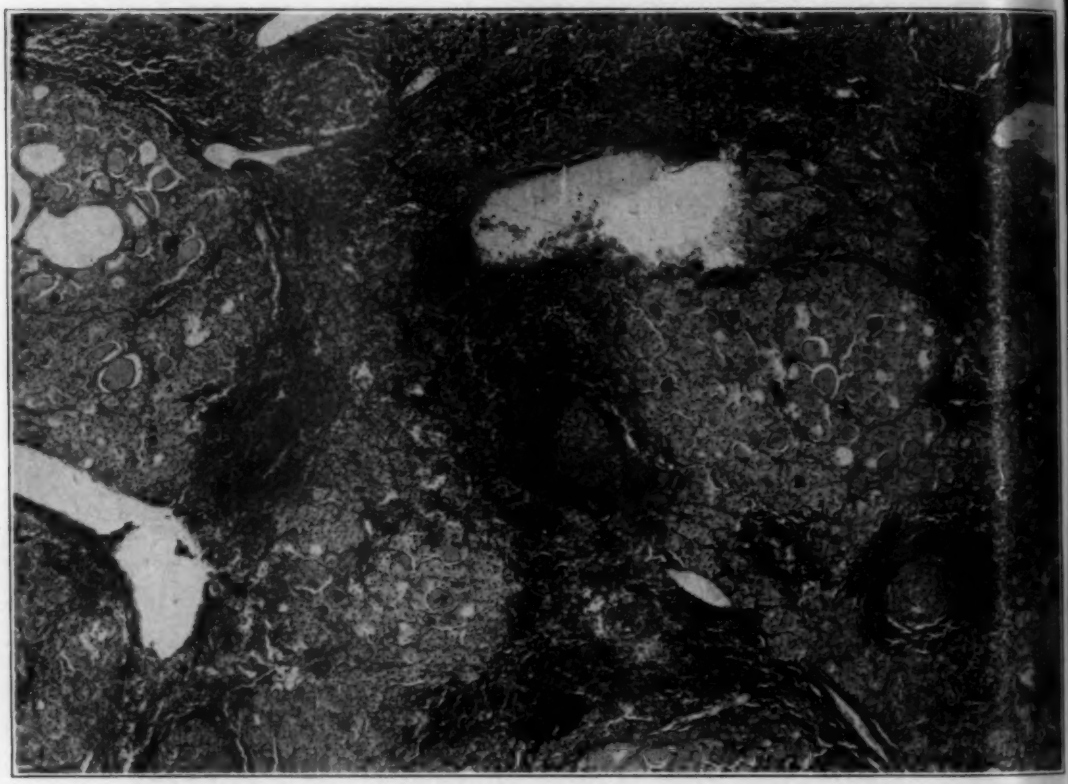

Fig. 3 (case 2).—Photomicrograph (× 50) of a section from the thyroid gland, showing the lymphoid follicles which are practically always present in large numbers with large germinal centers, in which there is active proliferation. In this slide there is also some normal thyroid tissue which is being infiltrated by lymphocytes. This is an early case.

thyroid tissue. Although frequently confused with Riedel's struma, in no instance to our knowledge has it been associated with a malignant process or developed into a malignant process.

We have operated on nine patients with goiter in the past two years who have been found by the pathologist to have struma lymphomatosa.

The clinical symptoms and laboratory findings of these nine patients have been very similar, but it is our feeling that rarely, if ever, are such results so distinctive that a preoperative diagnosis of the true condition can be made.

The nine patients in this series were women. The average age was 55.5 years. The twenty-four patients with Hashimoto's struma whose cases Graham [4] collected from reports in the literature were all women, and the average age was 52.4 years.

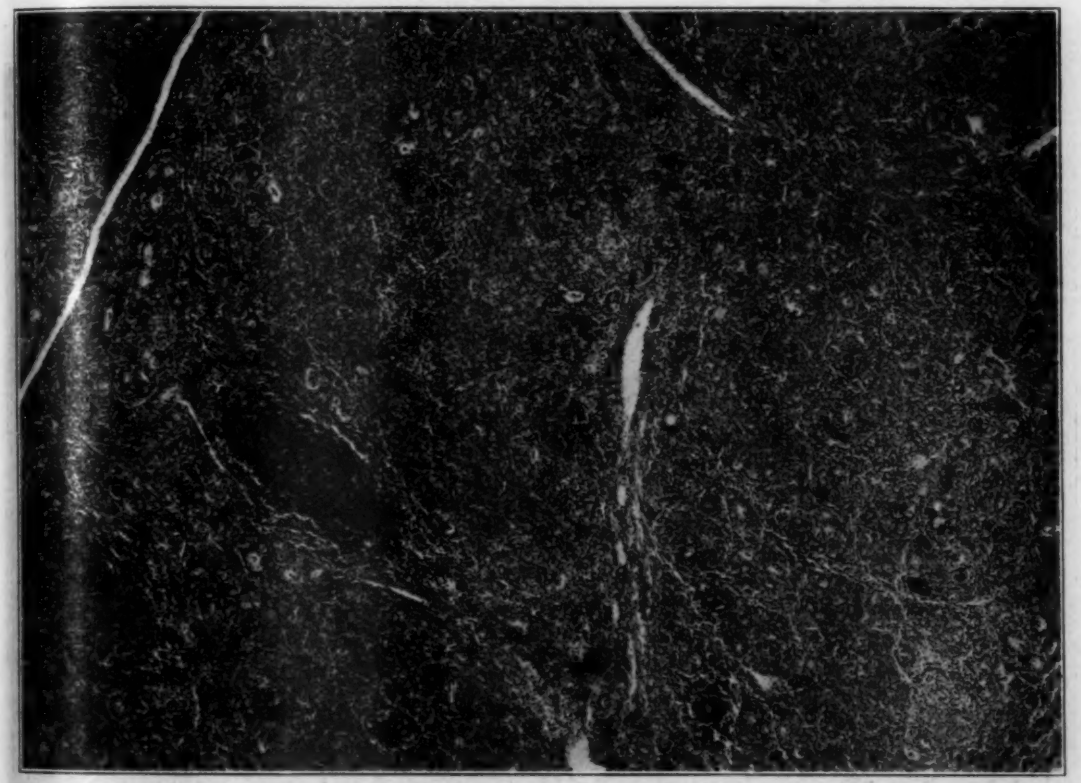

Fig. 4 (case 3).—Photomicrograph (× 50) of a section from the thyroid gland, showing thyroid alveoli but in markedly decreased numbers. There can be little function in the thyroid tissue.

The chief complaint of seven of the nine patients in our group was the presence of the goiter, while pressure on the trachea was the leading symptom of six patients. In general, the gradual appearance of a goiter and the increasing discomfort from the pressure exerted as it grows in size cause most patients to come for treatment. In three of

4. Graham, A.: Riedel's Struma in Contrast to Struma Lymphomatosa, West, J. Surg. **39**:681 (Sept.) 1931; Cleveland Clin. Quart. **1**:60 (Jan.) 1932.

our patients some evidence of myxedema was already present at the time of entrance.

On examination a patient with struma lymphomatosa presents a diffusely and symmetrically enlarged thyroid gland from two to six times the normal size. The enlargement generally involves both lobes and the isthmus. Nodules may be palpated, but this is rare. The outstanding finding on clinical examination is the marked firmness or stony hardness of the gland. The resemblance of the condition of the

Fig. 5 (case 5).—Photomicrograph (× 100) of a section from the thyroid gland, showing a typical lymphoid follicle and the lymphoid infiltration among the remaining alveoli. The alveolar epithelium is low and pale, and there is desquamation of it into the alveoli and infiltration by leukocytes.

gland to that in Riedel's struma is so great that it is very doubtful if clinical differentiation is possible. The marked degree of hardness of the thyroid on palpation may suggest a malignant condition in these patients, but the retention of a normal contour of the thyroid and the absence of adherence to surrounding structures are usually sufficiently striking to rule out this diagnosis. No cervical adenitis is present in association with Hashimoto's struma.

The basal metabolic rate of patients with struma lymphomatosa is usually below normal. In three of our nine patients some clinical evidences of myxedema were noted before operation, and the basal rate was below normal in five patients. It is doubtless true that the duration of struma lymphomatosa and degree to which the thyroid acini are replaced by infiltrating lymphoid tissue will determine the amount of thyroid insufficiency noted. In only one patient was the basal rate above normal (+ 16) and the possibility of thyroid toxicity considered.

It is possible that occasionally a patient with this type of goiter may have mild hyperthyroidism early in the course of the disease. Such a condition is not rare in persons with other types of chronic thyroiditis and is strongly suggested by the symptoms of one of our patients (case 6).

Roentgenograms taken to show the trachea very often reveal a narrowing of this structure by the pressure of the enlarged lateral lobes or of the isthmus. The narrowing of the trachea has never been sufficient to cause stridor, but it has been sufficient to produce a constant sense of discomfort in most patients.

The chief reasons for operating on these patients are, first to relieve the pressure and, second, to make the true diagnosis of the goiter.

At operation fairly characteristic findings are present, and for the first time the surgeon may have suggestive evidence of the true type of goiter which he has encountered. The gland is enlarged from two to five times the normal size and is not adherent to the surrounding structures. In this respect it differs from the gland as it is encountered in chronic thyroiditis and malignant conditions. The gland is firm and grayish pink before it is removed. On section it is white and appears almost edematous in certain areas. Clamps placed in the gland express serous fluid as they are compressed. They hold only to the fibrous capsule of the gland or to the blood vessels in the glandular substance and readily cut through the lymphoid tissue in the body of the goiter.

The operative procedure in the clinic is to treat these patients just as one does patients with chronic thyroiditis of the Riedel type. The pretracheal thyroid tissue is excised widely so that all pressure from the thyroid isthmus on the trachea is relieved. If adequate expansion of the trachea is not obtained by this method, a subtotal thyroidectomy is performed. Large remnants are left on each side, since it is well known that the advancing infiltration of the lymphoid tissue in these cases eradicates the secreting acini of the thyroid and will result in myxedema.

Hashimoto performed subtotal thyroidectomy on his patients and recommended this procedure. In one of our patients (case 3) only the right lobe and isthmus were removed at the first operation, and myxedema developed. In two years, however, the left lobe grew to a large size and caused such symptoms from pressure that it was removed,

Summary of Clinical Observations on Nine Patients with Struma Lymphomatosa

Name	Sex	Age	Main Symptoms	Presence of Myxedema (Preoperative)	Narrowing of Trachea as Shown by Roentgenograms	Operative Findings	Type of Operation	Post-operative Complications	Presence of Myxedema (Post-operative)	Later Examination
1. B. S.	F	54	Goiter (2 months); dysphagia	Slightly marked pallor; basal metabolic rate, —16	Slight	Thyroid, 4 times normal size; normal contour; no adhesions	Subtotal thyroidectomy	0	Marked myxedema; thyroid extract prescribed	1 year and 10 months later, well except for some numbness of hands; thyroid normal; still on thyroid extract
2. S. L.	F	35	Goiter (1 year); sensation of pressure in neck	No signs; basal metabolic rate, —15	Moderate anterior pressure	Thyroid, 2 to 3 times normal size; very firm; no adhesions	Subtotal thyroidectomy	0	Marked myxedema; thyroid extract prescribed	1½ years later, tired and depressed; cholesterol, 202; still on thyroid extract
3. P. W.	F	47	(first operation) Goiter (3 years); choking spells; nervousness and fatigue	No signs	Narrowed moderately	Right lobe, 2 times normal size; firm and friable; no adhesions	Subtotal thyroidectomy on right side and removal of isthmus	0	Considerable myxedema; thyroid extract prescribed	
		49	(second operation) Goiter on left side (10 months); sensation of pressure	Marked signs; basal metabolic rate, —23; cholesterol, 245	Deviated to the right	Left lobe, 4 times normal size; glistening white; no adhesions	Subtotal thyroidectomy on left side	Recurrent paralysis on left side	Marked myxedema; thyroid extract prescribed	8 months later, comfortable; thyroid extract continued; no goiter; voice normal
4. I. G.	F	46	Constriction in neck and windpipe (1 month)	No signs; basal metabolic rate, —19; cholesterol, 168	Deviated to the right	Left lobe, 3 times normal size; right lobe, 1½ times normal size; hard and friable; no adhesions	Subtotal thyroidectomy on left side	0	Considerable myxedema; thyroid extract prescribed	10 months later, well; right lobe, 3 times normal size; left lobe, normal size; no symptoms; thyroid extract stopped

5. H. T.	F	61	Goiter (2 months)	No signs; basal metabolic rate, —10	Anterior pressure	Thyroid, 4 to 5 times normal size; nodular; muscles slightly adherent to anterior surface	Subtotal thyroidectomy on right side; partial on left side	0	Started on thyroid extract (postoperative); no myxedema	Roentgen treatment prescribed (postoperative); 6½ months later, well; no myxedema; no thyroid extract taken
6. G. K.	F	54	Nervousness and fatigue (2 months); palpitation; loss of weight	No signs; thought to be slightly thyrotoxic; basal metabolic rate, + 16	Anterior pressure	Thyroid, 2 times normal size; unusually firm; no adhesions	Subtotal thyroidectomy	0	Marked myxedema; cholesterol, 510 mg.; thyroid extract prescribed	3 months later, general condition good; basal metabolic rate, —2; still on thyroid extract
7. E. W.	F	51	Goiter since childhood; large for 2 years; pains in ears	Moderate	?	Thyroid, 2 to 3 times normal size; extremely hard; no adhesions	Partial resection	0	Considerable myxedema; cholesterol, 272 mg.; thyroid extract prescribed	4 months later, general condition fair; myxedema present; still on thyroid extract
8. C. P.	F	47	Goiter for many years; acute cholecystitis 2 months previously, goiter enlarged and harder ever since; stridor (2 months)	No signs; basal metabolic rate, +2	Anterior compression	Thyroid, 4 to 5 times normal size; hard; no adhesions	Resection; removal of isthmus	0	No myxedema	1 month later, general condition good; no myxedema
9. M. H.	F	56	Constriction in neck; dyspnea; hoarseness (1 month); goiter in depressed condition 3 years before; improved on thyroid extract	Slight; basal metabolic rate, —13	Lateral and anterior pressure	Thyroid, 3½ times normal size; firm; tense; juicy; no adhesions	Subtotal thyroidectomy	0	Considerable myxedema; basal metabolic rate, —31; cholesterol, 194 mg.; thyroid extract prescribed	Recent case

although myxedema was already present. In another patient (case 4) only the left lobe was removed and examination ten months later showed a marked increase in the size of the remaining lobe, which was very hard and firm. In view of these two cases it may well be that subtotal thyroidectomy is the operation of choice for patients with struma lymphomatosa even though it probably always will be followed by myxedema. The usual care necessary in all operations for goiter must be taken to avoid injuries to the recurrent nerves and to the parathyroids.

The postoperative course is generally smooth and uncomplicated. Brawny thickening of the deep cutaneous layers of the neck, however, persists for from four to six weeks after operation. This has been generally true of patients with all types of thyroiditis on whom we have operated.

In seven of our nine patients myxedema developed after operation, and it was thought to be present for a time in another patient. The one patient in whom myxedema did not develop had only an excision of the thyroid isthmus for the relief of pressure, and her condition has not been followed since operation. It is reasonable to anticipate myxedema following resection of thyroid tissue in these patients, and it is most important that they be forewarned that it may occur. In general it seems to us that these patients are better without the discomfort of the thyroid tumor and with the myxedema controlled by medication than they were before operation. Following the complete operation they are apparently perfectly well as soon as myxedema is controlled. There has been no return of the thyroid tumor in any of our patients after subtotal thyroidectomy.

SUMMARY AND CONCLUSIONS

1. Struma lymphomatosa (Hashimoto) is a rare type of chronic thyroiditis marked by a diffuse infiltration of the thyroid with lymphocytes. The pathology is reviewed.

2. The clinical course of the disease in nine patients having this type of goiter is reviewed. It is believed that rarely, if ever, can the diagnosis of struma lymphomatosa be made from clinical examination.

3. The chief disturbance is pressure of the goiter on the trachea. Removal of the isthmus alone may give relief, but continuance of the growth may occur and necessitate further operation. Subtotal thyroidectomy is probably the operation of choice.

4. Myxedema usually follows the subtotal removal of such a goiter and may occur with this disease in the absence of operation.

5. Subtotal thyroidectomy relieves the symptoms caused by pressure, and recurrence of the goiter after this procedure has not occurred.

6. Malignant degeneration in this type of goiter has not been observed among our patients.

CHRONIC THYROIDITIS

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In 1896 Riedel [1] described a disease of the thyroid gland characterized by subacute, progressive swelling and hardening of the gland and progressive difficulty in respiration. Since that time many cases of benign swelling of the thyroid gland have been reported under the name of Riedel's struma, woody thyroiditis, ligneous thyroiditis or chronic thyroiditis.

In 1912 Hashimoto [2] reported 4 cases in which the subjective symptoms and physical findings were similar to those reported by Riedel but in which the thyroid tissue was replaced by lymphoid tissue. He called this condition struma lymphomatosa. The symptoms of the two conditions are much alike, and cases which are similar to those reported by Hashimoto are frequently reported under the name Riedel's struma.

In 1931 Graham [3] analyzed the cases reported prior to that time. He found reports of 104 cases. Of these, he classified 41 as definite instances of Riedel's struma and 24 as of the Hashimoto variety; he considered 22 as cases of adenoma with fibrosis and inflammation, hyperthyroidism and atrophy and fibrosis, suppuration, tuberculosis and syphilis of the thyroid gland; in the remaining 17 the diagnosis was unverified.

The gross and microscopic pathologic changes, the postoperative course and the complications of operation are different in the two conditions, and it would seem correct to consider them as two different diseases.

In Riedel's thyroiditis there is a progressive, rapid swelling of the gland. Only one lobe is involved in 49 per cent of the cases. The gland may feel smooth or slightly irregular, and it is very hard. Soon there are signs of tracheal pressure; these progress and in the late stages lead to severe attacks of asphyxia, which may be fatal. The regional lymph glands are rarely enlarged. In moderately advanced cases the borders of the thyroid are hard to distinguish accurately because of adhesions. There is no involvement of the skin. In advanced cases, hoarseness, dysphagia, recurrent nerve paralysis and signs of involvement of the great vessels may be seen. Occasionally the gland

1. Riedel: Verhandl. d. deutsche Gesellsch. f. Chir. **25**:101, 1896.
2. Hashimoto, H.: Arch. f. klin. Chir. **97**:219, 1912.
3. Graham, A.: West. J. Surg. **39**:681, 1931.

is tender. The white blood cell count is usually from 10,000 to 15,000 per cubic millimeter. The Wassermann and tuberculin tests give negative results. The average age is 39 years, and 44 per cent of the cases occur in men.

At operation in cases of Riedel's struma inflammatory adhesions are found between the capsule and the adjacent strap muscles. These may be very hard, and it may be impossible to find any line of cleavage. The tumor grasps the trachea as in a vise. The adhesions are usually very vascular, but within the capsule the tissue is often relatively avascular. There may be involvement of the trachea, carotid artery, internal jugular vein and recurrent laryngeal nerve.

The surfaces made by cutting are yellow-white. Microscopically, the normal glandular structure is almost entirely replaced by connective tissue. There is an extension inward of the capsular connective tissue. In places foreign body giant cells are found surrounding small bits of colloid. The predominant cell is the connective tissue cell, but there is a variable amount of infiltration with lymphocytes and plasma cells. In some fields no normal thyroid tissue can be seen.

The disease described by Hashimoto is almost always found in women, only 1 case having been reported in a man.[4] The average age incidence is 53 years. The chief symptom is rapidly increasing swelling of the thyroid gland. It almost always involves both lobes. There are seldom any adhesions to the adjacent muscles. At operation the gland can be freed without great difficulty. It is hard and smooth or slightly nodular. It is enlarged, retaining the form of the normal thyroid gland. Pressure over the trachea may be moderate, but the gland can be freed without great difficulty. On section the gland is divided into lobules by dense fibrous trabeculae. It cuts with difficulty. Microscopically there are an extensive diffuse infiltration with lymphocytes and numerous localized areas of lymphoid tissue with hyperplastic germinal centers. A few multinucleated foreign body giant cells may be present. There is an increase in connective tissue, but the tissue resembles a lymph gland, and there is very little colloid or normal thyroid tissue.

The following tabulation gives the chief differential points:

	Riedel's Struma	Struma Lymphomatosa
Average age	39 years	53 years
Sex	44 per cent males	4 per cent males
Average duration of symptoms	11 months	14 months
Unilateral involvement	49 per cent	Rare
Markedly adherent	78 per cent	None
Tracheotomy	22.2 per cent	None
Deaths	6	None
Postoperative hyperthyroidism	19.9 per cent of 32 cases	58 per cent of 19 cases

4. Meeker, L. H.: Am. J. Path. **1**:57, 1925.

Ewing stated that struma lymphomatosa is an early stage of chronic woody thyroiditis. However, as Graham pointed out, it seems unlikely that struma lymphomatosa is an earlier stage, since it tends to occur in older persons and since it tends to involve both lobes, whereas in the supposedly later stage the involvement is unilateral in 49 per cent of the cases.

Graham expressed the opinion that Riedel's struma is a local inflammation in the thyroid, the general bodily state being affected only secondarily by reason of destruction of thyroid tissue, respiratory difficulty or injuries to important blood vessels and nerves. He described struma lymphomatosa as a local manifestation of a constitutional disorder of unknown etiology. In this condition there are degenerative changes in the thyroid rather than inflammatory changes, and ultimately they are accompanied by more definite inflammatory phenomena of a nonspecific nature. The lymphoid tissue, which is variable in amount and to a less degree in character, is nonspecific for struma lymphomatosa.

The differential diagnosis rests between malignant changes, syphilis and tuberculosis. In cases of carcinoma of the thyroid, if there is involvement of the adjacent structures there is almost always involvement of the skin.[5] Carcinoma tends to start in one lobule and does not involve an entire lobe or gland uniformly. It tends to be much more nodular. It is very sensitive to roentgen treatment, whereas chronic thyroiditis is not. If there is doubt about the condition's being carcinoma of the thyroid, it is likely to be chronic thyroiditis, according to Payr.[6]

Vogel[7] stated that syphilis of the thyroid may show a diffuse sclerosis or gumma. The latter is hard to differentiate from a tumor. Congenital syphilis is always associated with visceral lesions. In tertiary syphilis the thyroid is hard, but it is always smaller and does not present a surgical problem. The Wassermann test and therapeutic tests will help in the diagnosis.

Tuberculosis of the thyroid gland is always secondary, according to Vogel. The disease is either miliary, with multiple gray or grayish-white nodules throughout the gland, or of the caseonodular form with small abscesses. There is almost always evidence of systemic tuberculosis.

REPORT OF A CASE

Mrs. S., aged 40, entered the Presbyterian Hospital on Oct. 13, 1932, complaining of exhaustion for seven months, slight enlargement of the thyroid for fifteen years, with increasing enlargement, especially on the right side, for the

5. Smith, L. W., and Clute, H. M.: Am. J. M. Sc. **172**:403, 1926.

6. Payr, E. L.: Report of International Conference on Goiter, 1927, Bern, H. Huber, 1929, p. 103.

7. Vogel, W.: Ergebn. d. Chir. u. Orthop. **23**:317, 1930

past seven months; numbness and tingling of the hands and feet for six months, with swelling of the hands and feet in the morning for two months; hoarseness for six months; severe headaches over the entire head for several months, and daily fever for four weeks starting six months previously. The blood test for undulant fever was questionably positive on one occasion. The systemic history was normal except for the occurrence of hay fever, which had been markedly relieved by serum treatment three years before.

The physical examination revealed a moderately well nourished woman whose general physical condition was normal except for the fact that the thyroid was markedly enlarged, the right side more than the left. It was irregular in outline, and especially near the midline the consistency of the right lobe was unusually firm. It was not fixed. No large glands were palpable. There was an increased transverse dulness just below the suprasternal notch.

The laboratory findings were: temperature, normal; pulse rate, 44 to 80; respiratory rate, 16 to 20; hemoglobin, 88 per cent; red blood cell count, 4,240,000 per cubic millimeter; white blood cell count, 10,800; differential count, normal; blood pressure, 90 systolic and 66 diastolic; stool and urine, normal; Ewald's test, 45 per cent free acid and 70 per cent total acid; roentgenogram of chest, normal; sinus arrhythmia and myocardial damage on electrocardiograph tracing; metabolic rate, —22 and —24. The diagnosis by Dr. R. C. Brown was "a probable carcinoma of the thyroid."

Operation was performed on Oct. 17, 1932, by Dr V. C. David. A Kocher incision was made with transverse division of the strap muscles. The right upper pole was freed from the surrounding parts with difficulty, and the artery was ligated. Biopsy of the right lobe with frozen sections showed "probable carcinoma." Therefore, a complete thyroidectomy was carried out. This was difficult owing to the fact that the thyroid very intimately surrounded the trachea but nowhere involved it. Two cigaret drains were left through the strap muscles.

A report of the macroscopic examination was made by Dr. David: "A uniform hard, boardlike thickening of the entire thyroid gland, especially involving the right and left lobes, was present. All regions except the pyramidal lobe were involved in this thickening and stonelike hardness of the gland. The gland appeared white and cut with increased tension. No colloid was visible. There were no metastases to the surrounding areas."

The results of the microscopic examination were reported by Dr. H. A. Oberhelman: "The specimen, weighing 70 Gm., consists of the left and right lobes and the isthmus of the thyroid gland. The left lobe is entirely enclosed by a thin fibrous capsule. It is very hard and is made up of irregular nodules up to 3 mm. in diameter. The cut surface of the right lobe is grayish yellow, except in a region 1.9 cm. in diameter near the upper pole, which is brownish yellow, soft and well demarcated from the surrounding tissue. The remainder of the lobe is hard. In serial sections through the back wall of the gland near the upper pole there are two small bright red regions, one just beneath the capsule and the other within the substance of the gland. The isthmus is uniformly hard and yellow.

"In all microscopic sections there is marked replacement of glandular tissue by connective tissue. In most of the sections no acini are present. There is dense round cell infiltration in all areas with several germinal centers. About 5 per cent of the area contains acini. They vary in size up to 0.2 mm. They can scarcely be distinguished from the surrounding connective tissue. The epithelial cells have very little cytoplasm, and the lumens contain a dark red material.

"The diagnosis is Riedel's struma."

The postoperative course was as follows: maximum temperature, 100; temperature normal on the fourth day; pulse rate, 60 to 74; respiratory rate, 16 to 20. The patient left the hospital on the nineteenth postoperative day. As postoperative medication thyroid extract was given as follows: 2 grains (0.13 Gm.) every four hours for the first six days; 2½ grains (16 Gm.) twice a day from the seventh to the eleventh day, and 2½ grains daily from the twelfth to the sixteenth day. On the second postoperative day an almost constant severe head-

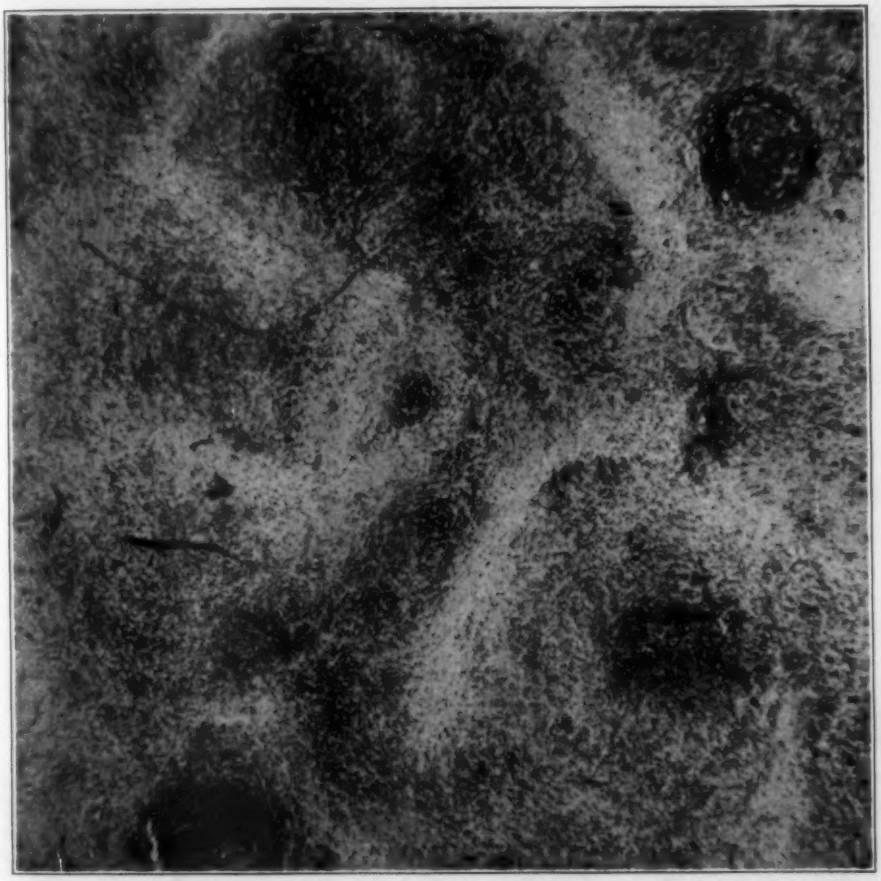

Fig. 1.—Photomicrograph (low power) showing predominance of connective tissue. Three areas of lymphoid hyperplasia are seen.

ache developed over the entire head. There were no signs of tetany. The serum calcium was 7.8 mg. per hundred cubic centimeters. The patient was given 1 cc. of parathyroid extract daily by hypodermic injection and ½ drachm (1.94 Gm.) of calcium lactate four times a day. On the third and fourth days the serum calcium was 8.5 mg. The headache was still present. The blood pressure was 90 systolic and 54 diastolic. The administration of parathyroid extract was stopped. The headache became more severe, and on the sixth day the serum

calcium was 8.7 mg. Parathyroid extract was again given for two days, with almost complete disappearance of the headache. On the fourteenth day the serum calcium was 9.5 mg., and the patient was receiving 1 cc. of parathyroid extract daily. When the patient was discharged the metabolic rate was —13 and the blood pressure was 98 systolic and 58 diastolic. She was discharged with the following medication prescribed: thyroid extract, 1 grain (0.064 Gm.) twice a day; calcium lactate, 30 grains, three times a day, and a preparation of parathyroid hormone, 1 cc. twice weekly.

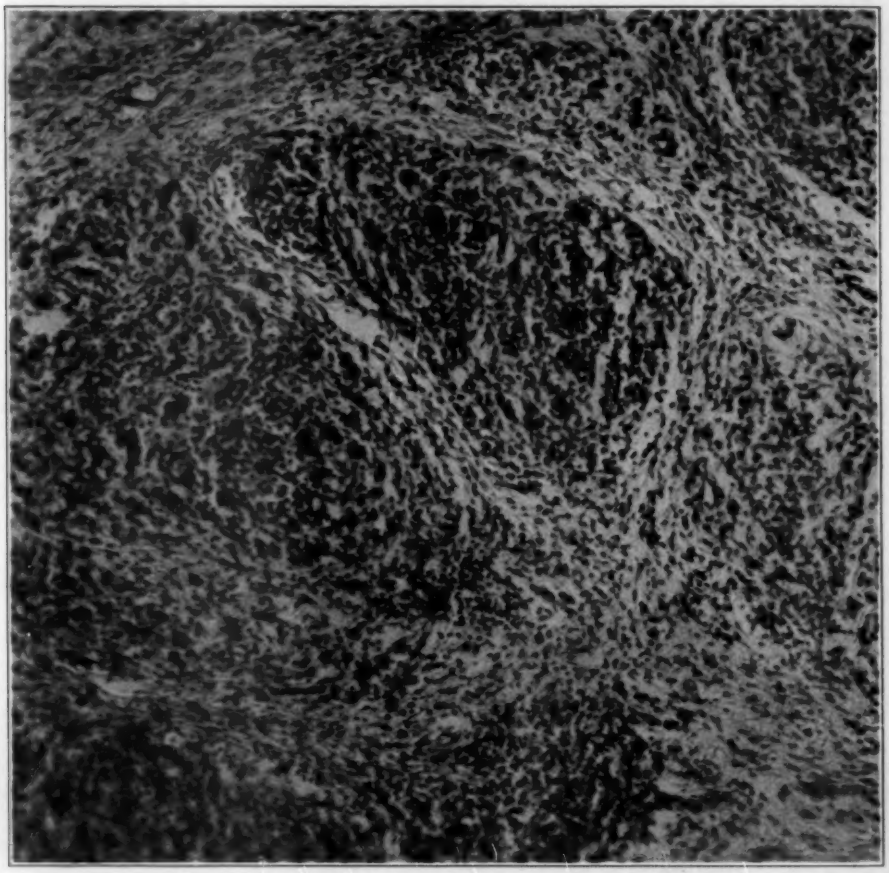

Fig. 2.—Photomicrograph showing extreme atrophy of glandular tissue and replacement by fibrous tissue and infiltration of plasma and round cells.

The patient was seen frequently after she left the hospital, and in January 1933, ten months after the operation, the metabolic rate was normal. She was taking thyroid extract, 1 grain three times a day. The blood calcium varied from 9 to 10 mg. She was taking calcium gluconate, 30 grains (1.9 Gm.) daily. Administration of the preparation of parathyroid hormone had been discontinued six months after she left the hospital. The blood pressure ranged from 90 systolic and 60 diastolic to 100 systolic and 68 diastolic. Headaches were infrequent but

were severe and of a migraine type. The hemoglobin content was 70 per cent; the red blood cell count, 4,400,000, and the white blood cell count, 8,000.

In October 1934, two years after the operation, she returned for treatment of migraine headaches, which were present almost daily. She had less endurance than before her operation but was able to lead a moderately active life. Transient numbness and tingling were present in her arms, hands and feet whenever she reclined. The pulse rate was from 56 to 78; the respiratory rate, from 16 to 20; the red blood cell count, 3,800,000; the hemoglobin content, 68 per cent; the white blood cell count, 8,300; the blood pressure, 104 systolic and 78 diastolic; the weight, 133 pounds (60.3 Kg.); the basal metabolic rate, —19; the serum calcium, 10.2 mg.; the result of the Ewald test, free acid, 35 per cent, and total acid, 55 per cent.

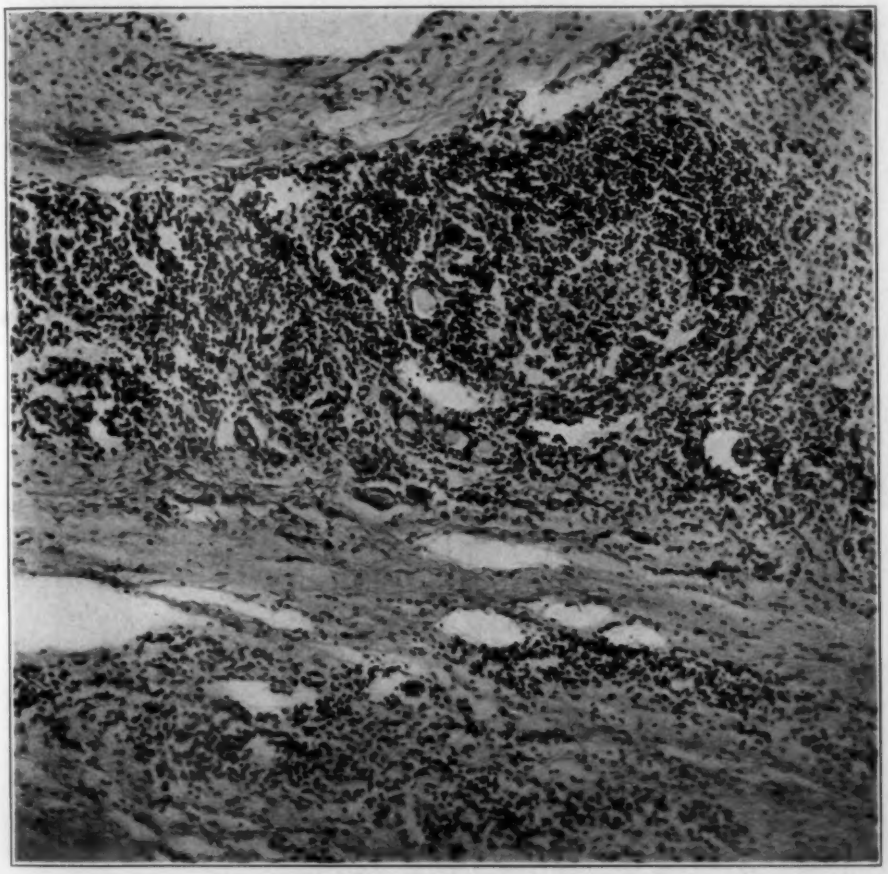

Fig. 3.—Photomicrograph showing one of the few areas containing colloid.

Most authors agree that a thin wedge-shaped resection of each lobe is all that is required, except for freeing the trachea if it is constricted. Recurrence of constriction after removal of tissue for biopsy or incision

is rare. Crile [8] and Payr advised high voltage roentgen therapy after operation, but Payr said that it is useless in cases of struma lymphomatosa. In view of the high incidence of postoperative hypothyroidism, it seems advisable to save a large part of the gland unless the preoperative basal metabolic rate is high.

8. Crile, G., and others: Diagnosis and Treatment of Diseases of the Thyroid Gland, Philadelphia, W. B. Saunders Company, 1932.

PHARYNGOGENIC HEMATOGENOUS STREPTOCOCCIC PERITONITIS

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A review of the literature on primary streptococcic peritonitis reveals a maze of conflicting opinions with regard to terminology, pathogenesis, general pathology and therapy. There is a dearth of data of accurately controlled experiments. It is with the expectation of clearing up some disputed points that we submit the following clinical, pathologic, immunologic and experimental study of eight cases of pharyngogenic hematogenous streptococcic peritonitis.

Pharyngogenic hematogenous streptococcic peritonitis is a metastatic inflammatory lesion of the peritoneum caused by a streptococcic hematogenous invasion from a primary focus in the tonsils and pharynx. The disease is characterized by an abrupt onset during or after the subsidence of an infection in the throat, great toxicity, short duration and usually fatal termination.

CLINICAL AND PATHOLOGIC STUDIES

In the following protocols only the relevant clinical and pathologic data are given.

REPORT OF CASES

CASE 1.—*History and Course.*—R. H., a married woman aged 33, was admitted to the hospital on March 3, 1934, with a history of pain of forty-eight hours' duration in the lower portion of the abdomen and in the loins, likened by the patient to "labor pains." There was persistent vomiting, but no bowel movement occurred for twenty-four hours. Five days prior to the onset of symptoms the patient had acute tonsillitis with subsequent complete subsidence of symptoms. On admission to the hospital the patient appeared to be acutely ill and distinctly dehydrated. The abdomen was distended and extremely tender, and there was a transverse band of rigidity across the midline. Spasticity of the abdominal wall was a prominent feature. The blood pressure was 70 systolic and 40 diastolic.

Operation by Dr. Auster on March 3 disclosed a large amount of thick, greenish-yellow pus in the abdomen and pelvis. The intestines were markedly hemorrhagic and moderately distended. Fibrinous plastic adhesions were present about the ileocecal region. The uterus and adnexa appeared to be intensely injected. Appendectomy with drainage was performed.

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Dr. A. B. Clements and Dr. W. Wolarsky assisted in the gross postmortem examinations.

The temperature, which on admission was 103.2 F., remained high, with a tendency to a slight increase in the peak each day until 105.6 and 107.6 F. were reached on the fourth and fifth day, respectively. The pulse rate varied between 130 and 160 and was of poor quality. Aspiration of the stomach yielded 1,000 cc. of dark brown fluid with a fecal odor. Death occurred on the fifth day of hospitalization, seven days after the onset of acute abdominal symptoms and two weeks after an attack of tonsillitis.

Laboratory Data.—The leukocyte count on March 3 was 15,000, with 85 per cent segmented forms, and on March 6, 8,600, with 88 per cent segmented forms. A blood culture on March 6 gave negative results. On March 3 and 6 albumin, red and white blood cells and hyaline and granular casts were noted in the urine. A culture of pus from the abdomen yielded Streptococcus alpha (viridans).

The appendix was 4 cm. in length. The vessels were prominent. Many petechial hemorrhages were present on the serosal surface, which was covered with purulent exudate. Sections showed intense hemorrhagic and purulent periappendicitis with invasion of the muscular coat.

Postmortem Examination.—The anatomic diagnosis was diffuse plastic peritonitis, ulcerative jejunitis, colitis and congestion of the lungs, liver and spleen.

The peritoneal cavity was filled with a thick, greenish-yellow plastic exudate and a thinner yellowish fluid. Recent fibrinous adhesions were present between the visceral and parietal peritoneum. Loops of intestine were bound together by exudate. There was no evidence of formation of an abscess. The small intestine was distended, and in the jejunum there were three transversely situated reddened ulcerated areas surrounded by an adherent greenish-yellow membrane. The large intestine was distended and congested. Throughout the colon, but most marked in the descending and sigmoid portions, were many superficial areas of ulceration, each surrounded by an adherent greenish-yellow membrane. The appendicular stump exhibited no noteworthy pathologic change.

Histopathologic Observations.—The pulmonary capillaries and arterioles exhibited marked congestion. The liver showed extensive hydropic degeneration of the parenchyma, chiefly at the periphery of the lobules. Massive hyaline thrombosis was present in the splenic pulp. The renal glomerular tufts were congested, and the tubules were intensely hemorrhagic. Marked hemorrhagic oophoritis was present with a periovarian extracapsular purulent exudate.

CASE 2.—*History and Course.*—N. N., a boy aged 4½ years, was admitted to the hospital on May 6, 1934, with a history of sore throat and fever for seven days and otitis for four days. On the second day of illness the temperature was 106 F. For the preceding two days epistaxis was noted.

On admission the child appeared acutely ill. The throat was red, and the cervical lymph nodes were enlarged and tender behind the angle of the jaw on both sides. The right ear drum was red and bulging and there was a slight bloody discharge. A myringotomy was done a few hours after admission. During the night the patient vomited and had several loose bowel movements, following which there developed a typical acute condition in the abdomen. The temperature, which on admission was 103 F., rose to 105.6 F.

On the following day an exploratory operation was performed by Dr. S. Cohn. Over the entire peritoneum, between the intestinal coils, beneath the liver and in the pelvis was a thick creamy purulent exudate. The lymph nodes in the ileocecal region were enlarged to approximately 2 by 1.5 cm. The appendix appeared to be involved by contiguity. Appendectomy with drainage was performed.

The postoperative course was characterized by profound toxemia. The temperature ranged between 103 and 105.2 F., with an average of approximately 104 F.

The pulse rate varied between 120 and 168. Death ensued on the fourth day of hospitalization, four days after the onset of acute abdominal symptoms and eleven days after an attack of sore throat. It may be of interest that multiple watery stools were noted during the entire stay in the hospital, often as many as five during the night. On the day preceding death the body was covered with a toxic rash.

Fig. 1 (case 2).—Intestinal lesions. Note the multiple focal hemorrhagic areas of necrosis and hyperplastic Peyer patches.

Laboratory Data.—The leukocyte count on May 6 showed 30,100, with 86 per cent segmented forms. On May 9 albumin, acetone and granular casts were noted in the urine. A culture of the peritoneal fluid yielded Str. alpha (viridans).

The appendix was 6 cm. in length. The serosal vessels were prominent; the coat appeared to be injected. Sections showed periappendicitis with marked con-

gestion. Hemorrhagic infiltration of the mucosa with free blood in the appendicular lumen was noted.

Postmortem Examination.—The anatomic diagnosis was diffuse plastic peritonitis, acute perisplenitis, acute hemorrhagic enterocolitis, mesenteric adenitis and bilateral bronchopneumonia.

The abdominal cavity contained straw-colored fluid, and covering the intestines was thick, yellowish, flaky, purulent exudate. In the region of the cecum were many fresh fibrinous adhesions. The mesenteric nodes were enlarged throughout the abdomen. The spleen was covered by a thick, yellowish, purulent membrane. On section the organ was dark red and hemorrhagic and the malpighian corpuscles were prominent. The intestines, beginning with the proximal portion of the

Fig. 2 (case 2).—Photomicrograph of an intestinal lesion. Note the triangular area of hemorrhagic necrosis with the base on circular muscularis. The ulcerated mucosa has been cast off.

jejunum, exhibited a diffusely hemorrhagic mucosa, and Peyer's patches were greatly enlarged. The most advanced lesions were seen in the terminal portion of the ileum, where numerous circumscribed, raised hemorrhagic nodules from 5 to 10 mm. in diameter were noted. They occurred most abundantly near the ileocecal valve. Some of the areas presented early necrotic changes. At the ileocecal junction were five hyperplastic, necrotic lymph nodules with crenated borders. Just within the ileocecal ring and in the cecum were a large hemorrhagic area and one necrotic lesion measuring 3 by 3 mm. The mucosa of the rectosigmoid presented a hemorrhagic appearance.

Cultures taken post mortem of the abdominal fluid, swabbings of the throat, heart blood, spinal fluid, feces and bone marrow yielded Str. alpha (viridans).

Histopathologic Observations.—Pulmonary edema was present, and many "heart failure" cells were noted. The parenchyma of the liver was the seat of

cloudy swelling, and the sinusoids were congested. The spleen exhibited congestion and edema of the splenic pulp with a suggestion of early formation of an infarct. In the kidneys bacterial emboli plugged the afferent vessels of some glomeruli, and many of the capillary tufts were blocked with bacteria. Many tubules were filled with similar clumps of organisms. One mesenteric node showed marked edema of the stroma with wide separation of the reticulum. The myocardium exhibited definite interfascicular edema.

CASE 3.—*History and Course.*—R. R., a boy aged 3 months, was admitted to the hospital on April 27, 1934, with a history of fretfulness and movement of the thighs suggestive of abdominal pain of four days' duration. For the preceding twenty-four hours distention was present. The temperature was 104 F.

On physical examination injected tonsils and pharynx, abdominal distention and rigidity were noted. Roentgenographic examination of the chest by Dr. Snow gave negative results, but the small intestine was distended with gas and exhibited fluid levels with the infant in the erect position suggesting obstruction in the small intestines.

Exploratory laparotomy seven hours after admission revealed distended intestines with free seropurulent fluid and flakes of fibrin in the peritoneal cavity. This was particularly evident about the ileocecal angle and appendix, where a thick, yellowish-green, plastic exudate was noted. Incision and drainage were done.

Following the operation the temperature remained at 105.2 F. The patient died four hours after the operation on the day of admission to the hospital and five days after the onset of the acute illness.

Laboratory Data.—The blood count on April 27 showed 24,500 leukocytes, with 6 per cent mature polymorphonuclears, 3 per cent young metamyelocytes, 54 per cent band forms, 35 per cent small lymphocytes and 2 per cent monocytes. A culture of the pus from the abdomen yielded Str. alpha (viridans).

Postmortem Examination.—The anatomic diagnosis was plastic peritonitis, perisplenitis, perihepatitis, mesenteric adenitis and multiple focal hemorrhagic lesions of the ileum and cecum.

The peritoneum was covered with a thick, yellowish, plastic exudate. The mesenteric lymph nodes were enlarged. The ileum appeared congested and exhibited many small focal hemorrhagic areas. The cecum showed similar lesions. The intestines were greatly distended with fluid feces and were matted together with a thick plastic exudate. The spleen and liver were covered with similar deposits. Str. alpha (viridans) was recovered from swabbings of the throat, abdominal fluid and heart blood.

Histopathologic Observations.—The pulmonary capillaries and arterioles were intensely congested, and an infarcted area was noted. The liver sinusoids were moderately congested. There were edema and hemorrhagic infiltration of the splenic pulp. The renal tissue exhibited acute hemorrhagic nephritis with swelling of the tubular parenchyma and endothelium of the capillary loops.

CASE 4.—*History and Course.*—S. M., a girl aged 2½ years, was admitted to the hospital on April 15, 1934, with a complaint of sore throat, abdominal pain, vomiting and fever. Seven days previously the patient had sore throat accompanied by general soreness and vomiting. The symptoms cleared up shortly, but four days later there was a recurrence in which abdominal pain was a prominent feature.

Physical examination disclosed an intensely reddened throat and tonsils which were covered with a punctate exudate. A nasal discharge was present. The entire abdomen was rigid and tender. The child looked acutely ill.

At operation by Dr. S. Cohn on the day of admission to the hospital the abdomen was filled with a large amount of thick, creamy pus and large fibrinous clots. The appendix was inflamed by contiguity and covered with a purulent, plastic exudate. All the mesenteric lymph nodes were greatly enlarged. Appendectomy with drainage was performed.

The postoperative course was rapidly downhill. A mild convulsive seizure occurred on the day following the operation. Cyanosis of the arms and legs was noted. Death occurred on the second day of hospitalization, five days after the onset of acute abdominal symptoms and nine days after the first complaint of sore throat.

The temperature on the day of admission gradually rose from 102.8 to 104.4 F. with continued increase on the following day until 107.8 F. was reached shortly before death. The pulse rate varied between 144 and 164 and the respiratory rate from 48 to 90.

Laboratory Data.—The blood count on April 15 showed 32,400 leukocytes, with 95 per cent segmented forms. A culture of the pus from the abdomen yielded Str. alpha (viridans). Roentgenographic examination of the chest by Dr. Snow gave negative results.

The appendix was 4.5 cm. in length. The serosal vessels at the tip were injected, and the distal half of the canal was obliterated. Sections showed acute periappendicitis. There were also edema and congestion of the mucosa.

We were unable to secure consent for a postmortem examination, so the studies on animals were limited to those made with the peritoneal organism.

Case 5.—*History and Course.*—E. B., a girl aged 8 years, was admitted to the hospital on Jan. 20, 1934, with a complaint of generalized abdominal pain which began abruptly eight hours previously and was unaccompanied by nausea or vomiting. On the day prior to admission the child complained of sore throat, and the condition was verified by the family physician, Dr. Rosenthal.

On admission the child appeared acutely ill. The tongue was coated and dry. The abdomen was rigid, and there was exquisite tenderness on light palpation in both lower quadrants.

Surgical intervention by Dr. J. Landy on the day of admission disclosed diffuse purulent peritonitis, most of the pus being situated in the pelvis. The appendix did not appear to be involved, but on opening it an irregular, superficial, oval ulcer was found in the mucosa extending down to the submucosal layer from which a drop of pus was expressed. There were two other well defined necrotic areas nearby. The postoperative course was very stormy. The abdomen became distended; the patient vomited greenish-yellow foul material repeatedly and was irrational. Two days after the first operation a jejunostomy was performed for paralytic ileus. A transfusion of 250 cc. of blood was given. The respirations became more shallow and of the Cheyne-Stokes type. The patient was in a state of profound shock and died on the fourth day of hospitalization, approximately four days after the onset of acute abdominal symptoms and five days after the angina was noted. It is of interest that on the second day postoperatively the child complained of pains in the joints, and held the neck rigid on being moved.

The temperature varied from 104 F. prior to admission to the hospital to 107 F. shortly before death. The pulse rate varied between 120 and 150.

Laboratory Data.—The leukocyte count on January 20 showed 18,000, with 90 per cent segmented forms. A culture of the peritoneal fluid revealed Str. alpha (viridans).

Permission for postmortem examination could not be obtained.

CASE 6.—*History and Course.*—M. C., a boy aged 6 months, was admitted to the hospital on March 8, 1934, with a history of a cough and inflamed throat for five days, during which the temperature fluctuated between 101.2 and 105 F. Eight hours before admission the family physician noted rigidity of the abdomen.

Physical examination revealed an infant acutely ill. The throat was congested, and cervical adenopathy was present. Edema of the scrotum and hydrocele were noted.

Operation.—A few hours after admission an abdominal paracentesis yielded seropurulent fluid which was cultured. On the following day a laparotomy was done by Dr. J. Landy, and free pus was found in the abdomen. Drainage was instituted, but the patient died on the second day of hospitalization, approximately three days after the onset of acute abdominal signs and one week after angina was noted. The temperature during hospitalization varied from 103.8 on admission to 105.8 F. shortly before death. The respiratory rate on the last day varied between 50 and 100. Abdominal distention, vomiting and twitching of the body were prominent features of the preoperative and postoperative periods.

Laboratory Data.—The blood count on March 7 showed hemoglobin, 70 per cent; erythrocytes, 3,750,000, and leukocytes, 14,000, with 22 per cent band forms and 60 per cent mature polymorphonuclears. The urine on March 7 contained albumin. A culture of the abdominal fluid on March 8 revealed Streptococcus gamma (nonhemolytic).

Postmortem Examination.—The anatomic diagnosis was generalized peritonitis, bronchopneumonia, edema of the scrotum and hydrocele.

The spleen and liver were covered with a thick, greenish-yellow purulent exudate. The intestines were matted together by the same material. The appendix appeared to be normal.

Histopathologic Observations.—Sections of pulmonary tissue showed bronchopneumonia with marked capillary and arteriolar congestion and hemorrhagic pleuritis. There was cloudy swelling with hydropic degeneration and fragmentation of the cords of the liver. The sinusoids were congested. Congestion of the splenic pulp and acute diffuse, nonhemorrhagic nephritis were present.

Cultures made of swabbings of the throat and heart and abdominal fluid were grossly contaminated, and the Streptococcus could no longer be recovered.

CASE 7.—*History and Course.*—M. L., a woman aged 29, was admitted to the hospital on March 10, 1934, in the first stage of labor. A history was obtained of sore throat at frequent intervals during the past month, the last attack having been one week before admission to the hospital. A Porro cesarean section was performed three days after admission. Culture from the uterus showed Str. gamma (nonhemolytic).

On the second day postoperatively signs of peritonitis were noted. The clinical course was rapidly downhill in spite of an emergency supracervical hysterectomy, and death occurred on the ninth day of hospitalization, six days postoperatively and thirteen days after a sore throat. Four transfusions, each of 350 cc. of blood, were given without avail.

It is noteworthy that on the first three days of hospitalization the temperature varied between 99 and 100.4 F. Five hours before the Porro cesarean operation, the patient had a chill and the temperature rose to 103.2 F. The postoperative temperature varied between 101 and 107 F., with an average of 106 F. during the three days preceding death.

Laboratory Data.—The blood count on March 17 showed hemoglobin, 66 per cent, erythrocytes, 3,700,000, and leukocytes, 18,400, with 24 per cent band forms

and 60 per cent mature polymorphonuclears. Two blood cultures were negative. The urine on March 17 contained albumin, erythrocytes and leukocytes.

Postmortem Examination.—The anatomic diagnosis was pelvic peritonitis, ulcerative colitis and proctitis, congested spleen, chronic adhesive pleurisy, bilateral, and acute metritis.

Pelvic peritonitis was fairly well localized to the surgical field. No vascular thrombosis or phlebitis was noted. Some of the loops of the small intestine were adherent and covered with necrotic, grayish purulent membrane. In the region of the sigmoid flexure and rectum were seen many ulcerated areas on the mucosa.

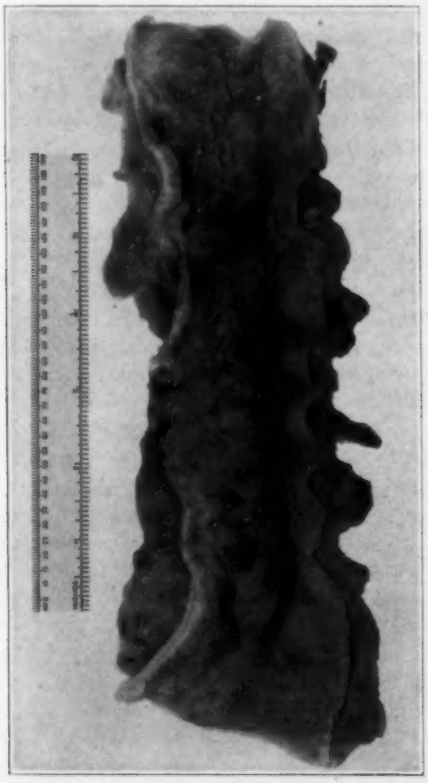

Fig. 3 (case 7).—Multiple focal areas of necrosis in the intestine.

These were shallow, from 2 to 3 cm. in diameter, circular and surrounded by a greenish fringe of purulent membrane which could not readily be removed. The peritoneal organism was a nonhemolytic streptococcus.

Histopathologic Observations.—The sinusoids of the liver were moderately congested. A splenic infarct was present. The renal tissue showed acute hemorrhagic nephritis with thrombi in some of the smaller arterioles. The myocardium exhibited interfasicular edema and some fibrosis. The vessels in the ovary were congested, and the uterus gave evidence of acute metritis which appeared to start from the peritoneal aspect in the region of the operative wound.

CASE 8.—*History and Course.*—E. F., a woman aged 34, was admitted to the hospital on March 2, 1934, with a complaint of diffuse abdominal pain and nausea of two days' duration. The temperature varied between 104 and 105 F. On the day of admission the pain became more intense and appeared to be localized to the lower portion of the abdomen. The patient had had sore throat approximately one week before admission. She appeared to be acutely ill. The entire abdomen was rigid, and tenderness was most marked in the right lower quadrant.

Surgical intervention by Dr. Amster on the day of admission disclosed free pus in the abdomen. The omentum was wrapped around the cecum and adjoining loops of small bowel. The appendix appeared to be normal. The postoperative course was stormy. The patient was delirious, complained of dysphagia and died on March 6, approximately two weeks after an attack of sore throat and six days after the onset of acute abdominal symptoms.

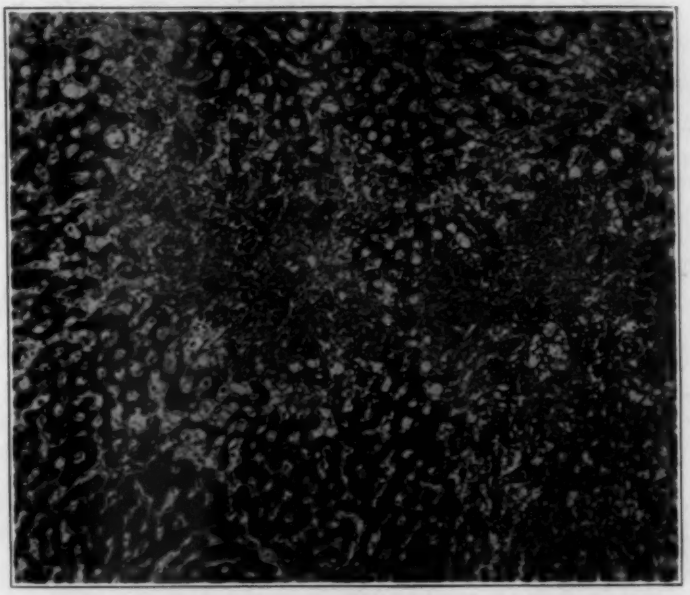

Fig. 4 (case 8).—Photomicrograph of multiple necrotic lesions of the parenchyma of the liver.

The temperature on admission was 105.2 F. and averaged 104 F. during the entire period of hospitalization. The pulse rate varied from 120 to 144 and the respiratory rate from 26 to 42.

Laboratory Data.—The leukocyte count on March 3 showed 47,000, with 83 per cent segmented polymorphonuclears, 15 per cent band forms and 2 per cent lymphocytes. The urine on March 3 and 5 contained albumin and some leukocytes. A culture of the abdominal pus yielded Str. gamma (nonhemolytic).

The appendix was 5 cm. in length and was covered with a thin fibrinous exudate. The sections showed early acute periappendicitis.

Postmortem Examination.—The anatomic diagnosis was generalized peritonitis, splenic infarcts, renal abscess and pleurisy on the right side.

The peritoneal cavity was filled with a plastic purulent exudate and a thinner purulent fluid. Recent fibrinous adhesions were seen everywhere, particularly in

the cecal and sigmoid regions. The loops of intestine were matted together. Perihepatitis and perisplenitis were noted. There was no localized formation of abscess, and the subphrenic spaces were clear. The right kidney exhibited a cortical abscess the size of a pinhead. The stomach was greatly distended and covered with a purulent exudate. There was moderate enlargement of the mesenteric nodes. Both lungs were congested at the base, and the right pleura was covered with a purulent membrane.

Histopathologic Observations.—Sections of pulmonary tissue showed intense vascular congestion and edema. In the liver were scattered areas of hydropic degeneration, chiefly at the periphery of the lobules, and the sinusoids were congested. There were edema, congestion and hyaline thrombi in the splenic pulp. The vessels in the wall of the fallopian tube were intensely congested.

TABLE 1.—*Results of Inoculation of Rabbits with Organisms Recovered from the Patient in Case 1*

Rabbit	Source of Str. Viridans	Dosage, Cc.	Days	Result	Histopathologic Observations
5	Peritoneum	(1) 3	4	Organism recovered from feces; diarrhea	Focal necroses in liver
		(2) 6 (13th day)	1	Positive blood culture	
		(3) 6 (23d day)	4	Positive blood culture	
			6	Fatal; organism recovered from pericardial sac, peritoneum and heart blood	
99	Peritoneum	3	8	Killed; necrotic lesions in ileum; organism recovered from feces	Intestinal lymphoid hyperplasia with central necrosis of solitary nodules
66	Peritoneum	3	2	Killed; superficial ulcers in ileum	
28	Peritoneum	7: toxin	..	No effect	

STUDIES IN ANIMALS

In the studies on animals certain objectives were kept in mind in each experiment which are indicated in the protocols. Preliminary control tests were made on each animal before inoculation. Eighteen hour broth cultures and the intravenous route were used except when otherwise specified.

CASE 1.—The organism recovered from the peritoneal fluid was used.

Rabbit 5.—Three cubic centimeters of an eighteen hour broth culture was injected. The organism was recovered from the feces on the fourth day when slight diarrhea was noted. On the thirteenth day a second inoculation of 6 cc. was made. Twenty-four hours later the blood culture was positive. The rabbit survived, and on the twenty-third day a third inoculation of 6 cc. was made. After four days the blood culture was positive, and the animal died two days later. Postmortem examination revealed that the pericardial sac contained 25 cc. of flaky, purulent exudate, the abdomen was filled with 40 cc. of blood-tinged, flaky, purulent exudate most evident in the hepatic and splenic areas, and the liver was dark red and congested. The organism which had been injected was recovered from the pericardial sac, peritoneal cavity and heart blood. Sections of the liver showed multiple focal necroses most marked in the lobules nearest the capsule. The sinusoids were dilated with clear fluid. The spleen exhibited edema of the pulp.

Rabbit 99.—Three cubic centimeters of a broth culture was injected intravenously. The animal was killed eight days later. Small necrotic areas were found in the ileum. The organism which had been injected was recovered from the feces. Sections of the intestine showed marked lymphoid hyperplasia with small areas of central necrosis in the solitary nodules.

Rabbit 66.—Three cubic centimeters of a broth culture was injected intravenously. Slight diarrhea was noted, and the animal was killed after forty-eight hours. A few superficial ulcer-like erosions were noted in the ileum.

TABLE 2.—*Results of Inoculation of Rabbits with Organisms Recovered from the Patient in Case 2*

Rabbit	Source of Str. Viridans	Dosage, Cc.	Days	Result	Histopathologic Observations
72	Throat	8: intravenously	2	Organism recovered from feces; survived	
48	Peritoneum	7: orally	7	Organism recovered from feces; survived	
57	Peritoneum	13: by rectum	7	Organism recovered from feces; survived	
19	Peritoneum	4: toxin intravenously	21	Diarrhea; congestion of small intestines	Portal congestion of liver
39	Peritoneum	8: intravenously	5	Diarrhea; fatal; organism recovered from throat, feces, peritoneum, spleen, liver, spinal fluid, pericardial fluid; ulcerative and hemorrhagic lesions in ileum and appendix; purulent pericarditis; peritonitis	Lymphoid hyperplasia with slight central necrosis
30	Heart blood	5: intravenously	5 15	Diarrhea Fatal; organism recovered from throat, peritoneum, pericardium, liver, spleen, feces, spinal fluid and heart blood; purulent peritonitis; pericarditis; perihepatitis	Pulmonary edema; hemorrhagic pleuritis, focal necroses in liver
65	Feces	6: intravenously	6	Fatal; organism recovered from throat, peritoneum, pericardium, liver, spleen, feces, spinal fluid and heart blood; purulent peritonitis; pericarditis	
98	Spinal fluid	8: intravenously	12	Fatal; organism recovered from throat, peritoneum, pericardium, liver, spleen, feces, spinal fluid and heart blood; fibrinous pericarditis and peritonitis; focal hemorrhagic enterocolitis	

Rabbit 28.—Seven cubic centimeters of toxin (filtered eighteen hour broth culture) was injected with no untoward results.

CASE 2.—*Rabbit 72.*—The organism from the throat of the patient, in 8 cc. of bouillon culture, was injected intravenously. Forty-eight hours and four days later the organism was recovered from the feces.

Rabbit 48.—The peritoneal organism, in 7 cc. of bouillon culture, was administered orally. The organism was recovered in the feces one week later. The animal survived.

Rabbit 57.—The peritoneal organism, in 13 cc. of bouillon culture, was given by rectum. The organism was recovered from the feces one week later. The animal survived.

Rabbit 19.—Four cubic centimeters of the toxin of the peritoneal organism (eighteen-hour filtered broth culture) was injected intravenously. Mild diarrhea ensued. The animal was killed after twenty-one days, and congestion of the small intestines was noted. Sections of the liver showed moderate portal congestion, but no essential pathologic change.

Rabbit 39.—The peritoneal organism, in 8 cc. of bouillon culture, was injected intravenously. Diarrhea was noted, and death occurred in five days. The organism was recovered from the throat, feces, peritoneum, spleen, liver, spinal fluid and pericardial fluid. Early ulcerative lesions were noted in the

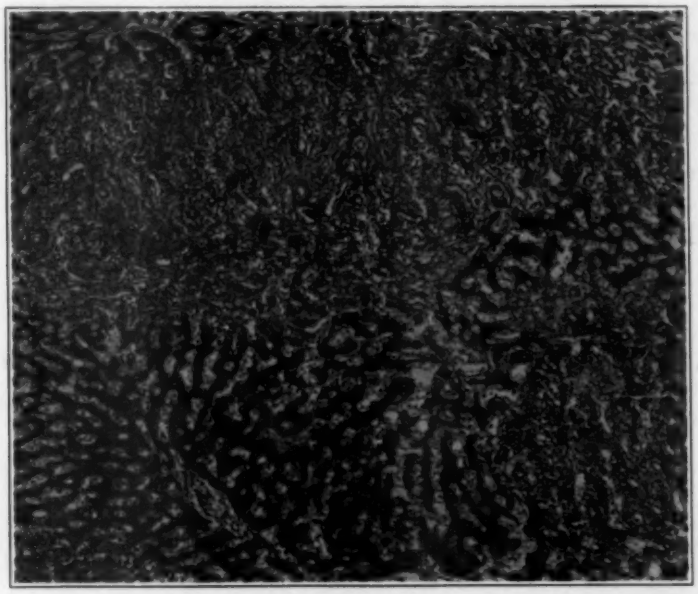

Fig. 5 (rabbit 30, inoculated with peritoneal organism from the patient in case 2).—Photomicrograph of multiple necrotic lesions of the parenchyma of the liver.

ileum and punctate hemorrhagic areas in the ileum and appendix. Purulent pericarditis and peritonitis were present. Sections of the intestine showed lymphoid hyperplasia and an enlarged mesenteric node with slight central necrosis.

Rabbit 30.—The organism recovered from heart blood, in 5 cc. of bouillon culture, was injected intravenously. At the end of the fifth day diarrhea was evident, and the rabbit appeared sickly. Profuse diarrhea followed, and the animal died on the fifteenth day. The organism was recovered from the throat, peritoneal fluid, pericardial fluid, liver, spleen, feces, spinal fluid and heart blood. Seropurulent fibrinous peritonitis, pericarditis and profuse purulent perihepatitis were noted. Sections of tissue of the lungs showed pulmonary edema and hemorrhagic pleuritis. In the liver were small focal necroses, most marked in the lobules nearest the capsule. In the spleen were focal areas of large macrophages laden with blood pigment.

Rabbit 65.—The organism from the feces, 6 cc. of bouillon culture, was administered intravenously. Death occurred in six days. The organism was recovered from the throat, peritoneal fluid, pericardial fluid, liver, spleen, feces, spinal fluid and heart blood. Seropurulent fibrinous pericarditis and peritonitis were present. The spleen was markedly congested.

Rabbit 98.—The organism from the spinal fluid, 8 cc. of bouillon culture, was injected intravenously. Death occurred in twelve days. The organism was recovered from the throat, peritoneal fluid, pericardial fluid, liver, spleen, feces, spinal fluid and heart blood. There were fibrinous peritonitis and

TABLE 3.—*Results of Inoculation of Rabbits with Organisms Recovered from the Patient in Case 3*

Rabbit	Source of Str. Viridans	Dosage, Cc.	Days	Result	Histopathologic Observations
17	Peritoneum	5: intravenously	3	Diarrhea; positive blood culture; organism recovered from feces	Lymphoid hyperplasia of mesenteric node with focal hemorrhagic areas
			5	Fatal; organism recovered from blood, feces and peritoneum; hemorrhages in terminal ileum	
59	Peritoneum	5: toxin intravenously	..	No effect	
		8: intravenously	18 hrs.	Diarrhea; fatal; organism recovered from throat, peritoneum, pericardium, feces, spleen and heart blood	
46	Throat	(1) 5: intravenously	1	Organism recovered from feces	
			3	Positive blood culture	
			7	Positive blood culture	
		(2) 6: intravenously (8th day)	1	Organism recovered from feces	
		(3) 8: intravenously (27th day)		Survived	
64	Throat	8: intravenously	2	Organism recovered from feces; survived	
25	Heart blood	5: intravenously	1	Organism recovered from feces	Areas of coagulation necrosis in liver; splenic infarct; hemorrhagic nephritis
			3	Fatal; organism recovered from blood, feces; ulcers in terminal ileum	

pericarditis and free fluid in the pericardium. The intestinal tract was greatly distended and injected. Focal hemorrhagic areas were noted in the small and large intestines. The kidneys appeared to be granular and edematous. Small whitish necrotic areas were seen in the auricles. Sections of the liver showed marked congestion of the central veins and sinusoids. The walls of some vessels were composed entirely of a thick, structureless, hyaline material suggestive of a degenerative or necrotic lesion. The splenic pulp was infiltrated with blood, and many macrophages loaded with blood pigment were present. The intestinal section showed a single thrombosed vessel.

CASE 3.—*Rabbit 17.*—The peritoneal organism, in 5 cc. of a bouillon culture, was given intravenously. Three days later the blood culture was positive, and the organism was recovered from the feces. Diarrhea appeared and increased until the rabbit died five days after the injection. The organism was recovered from the blood, feces and peritoneum. There was a diffuse fine hemorrhagic

speckling of the terminal ileum. Sections of the intestine exhibited no noteworthy pathologic change, but a mesenteric node showed lymphoid hyperplasia with marked edema and focal hemorrhagic areas.

Rabbit 59.—Five cubic centimeters of toxin (filtered eighteen hour broth culture) of the peritoneal organism was given intravenously without effect. The

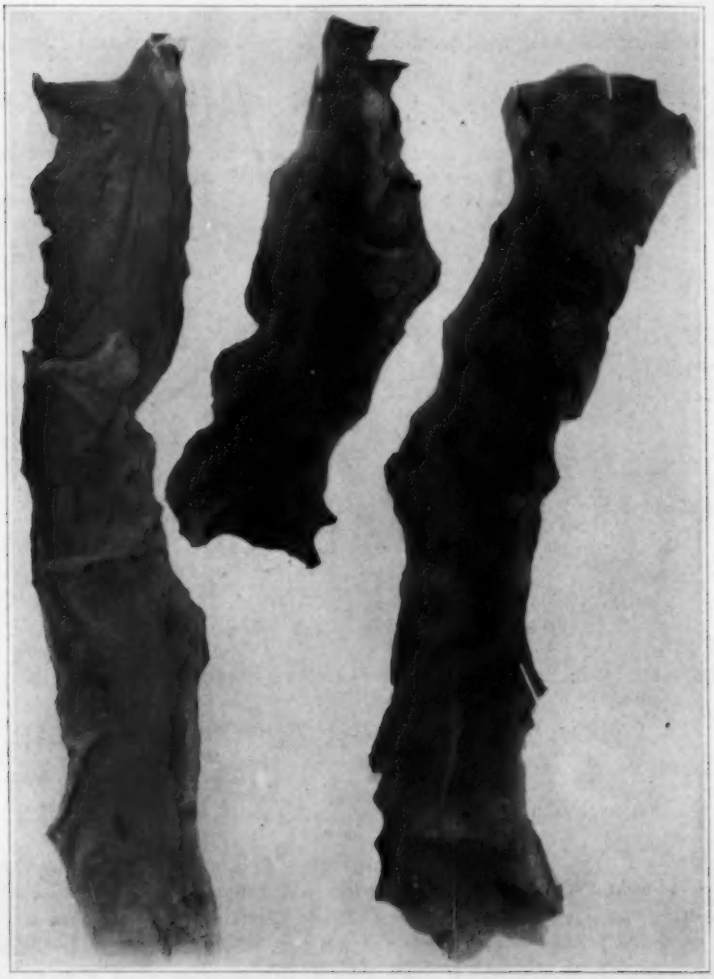

Fig. 6 (rabbit 17, inoculated with peritoneal organism from patient in case 3).—Multiple focal hemorrhagic areas of necrosis in the intestine.

animal was reinoculated with 8 cc. of a bouillon culture intravenously. Profuse diarrhea ensued, and death occurred in eighteen hours. Postmortem examination revealed a sanguinopurulent exudate in the peritoneal cavity; the intestines were distended, and the spleen appeared congested. Positive cultures were obtained from the throat, peritoneum, pericardium, feces, spleen and heart blood.

Rabbit 46.—The organism from the throat, in 5 cc. of a bouillon culture, was given intravenously. The following day the organism was recovered from the feces. On the third and the seventh day the blood cultures were positive. A second inoculation of 6 cc. was given on the eighth day. The organism was again recovered from the feces. On the twenty-seventh day a third inoculation of 8 cc. was given. The animal survived.

Rabbit 64.—The organism from the throat, in 8 cc. of bouillon culture, was injected intravenously. The organism was recovered from the feces two days later. The animal survived.

Rabbit 25.—The organism from heart blood, in 5 cc. of bouillon culture, was injected intravenously. On the following day the organism was recovered from the feces. Death occurred on the third day, and the organism was recovered from the blood, feces and ulcerated lesions in the terminal ileum. Sections of the liver showed small areas of coagulation necrosis about the central veins and near the

TABLE 4.—*Results of Inoculation of Rabbits with Organisms Recovered from the Patient in Case 4*

Rabbit	Source of Str. Viridans	Dosage, Cc.	Days	Result	Histopathologic Observations
34	Peritoneum	6: intravenously	2	Fatal; peritonitis; pericarditis; congestion of lungs; organism recovered from throat, peritoneum, pericardium, liver, spleen, heart blood, spinal fluid and feces	Diffuse parenchymatous degeneration of liver; multiple glomerular bacterial emboli kidney (same as in case 2)
90	Peritoneum	8: intravenously	2	Profuse diarrhea; fatal; fibrinous peritonitis; pericarditis; congested spleen; organism recovered from throat, peritoneum, pericardium, liver, spleen, heart blood, spinal fluid and feces	

capsule. In the splenic pulp were extensive hyaline thrombi with infarction. There was acute hemorrhagic nephritis with massive hemorrhages, shrunken glomeruli and parenchymatous degeneration.

CASE 4.—*Rabbit 34.*—The organism, in 6 cc. of broth culture, was injected intravenously. Death occurred in two days. The intestinal tract was greatly distended, and a small amount of free serosanguineous fluid was seen in the peritoneal cavity. There was a fibrinous exudate over the liver and the entire visceral and parietal peritoneum. A similar exudate was present in the pericardial sac. The lungs were congested. The organism was recovered from the throat, peritoneum, pericardium, liver, spleen, heart blood, spinal fluid and feces. Sections of the liver showed diffuse parenchymatous degeneration with clumps of bacteria in the sinusoids. There was cloudy swelling of the renal parenchyma with multiple glomerular bacterial emboli.

Rabbit 96.—The organism, in 8 cc. of broth culture, was given intravenously. Profuse diarrhea occurred, and death ensued in two days. The peritoneum was covered with a thin fibrinous exudate and the peritoneal cavity contained 10 cc. of serosanguineous fluid. The large intestine was greatly distended. The spleen was enlarged and congested. There was a thin fibrinous exudate in the pericardial sac. The organism was recovered from the throat, peritoneum, pericardium, liver,

spleen, heart blood, spinal fluid and feces. Sections of the liver showed diffuse parenchymatous degeneration. There were moderate congestion and edema of the splenic pulp.

IMMUNOLOGIC STUDIES

Having determined that the various strains of Str. viridans contained many similar features in their action on the animal host, we questioned the possibility of an antigenic similarity among all the strains. We felt that if this identity in antigenic structure could be demonstrated we might dispel such objections as coincidental finding of Str. viridans in a few cases, agonal infection or extraneous contamination.

If a serum containing antibodies to one of the strains would unite specifically with the other antigens this similarity in antigenic structure

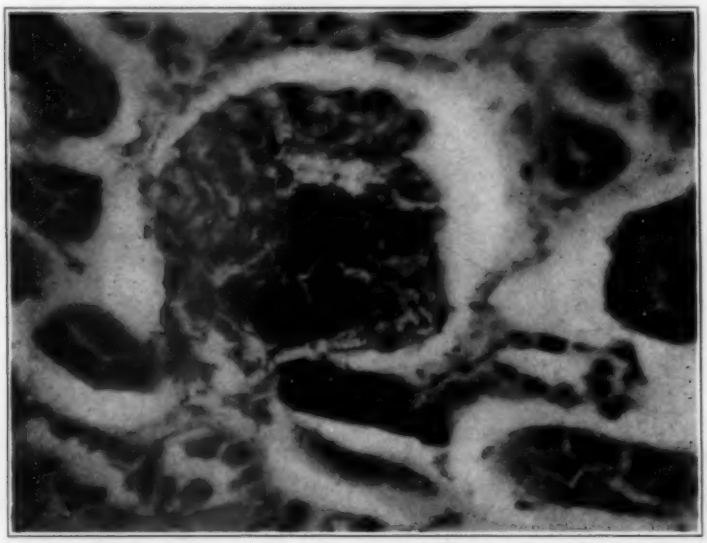

Fig. 7 (rabbit 34, inoculated with peritoneal organism from the patient in case 4).—Photomicrograph of a bacterial embolus in a glomerulus and afferent vessel.

would be established. We chose the complement-fixation test for this purpose because of its great sensitivity.

The actual experiment was conducted according to the protocol, and the reagents which were used were prepared as follows:

Complement.—Fresh guinea-pig serum was used. The titration was performed so that in a suitable dilution of the serum, 0.2 cc. contained 2 units.

Antigen.—The various antigens used are listed in table 6. They consisted of eighteen hour serum broth (p_H 7.8) cultures of the desired organism. In preliminary tests the anticomplemental action and hemolytic power of each antigen were titrated. It was found that 0.2 cc. of a 1:5 dilution of the culture in saline solution did not inhibit the action of the complement and was not hemolytic for the sheep cells.

TABLE 3.—*Clinical and Pathologic Observations on Eight Cases and Results of Experimentation on Animals in Four Cases*

Case and Age	No. of Days Angina Preceded Abdominal Symptoms	No. of Days Between Onset of Acute Abdominal Symptoms and Death	Organism	Temperature (Peak), F.	Blood Count on Admission*	Gross Pathologic Observations	Histopathology	Organism Recovered From	Animal Studies: Gross Pathologic Observations	Animal Studies: Histopathology	Animal Studies: Diarrhea	Animal Studies: Organism Recovered
1 33 yr.	7 days	7 days	Str. viridans	107.6	15,000 85	Peritonitis; periappendicitis; ulcerative jejunitis and colitis; hemorrhagic inflammation of the intestines, liver, spleen, kidneys, ovaries and lungs	Pulmonary congestion; degeneration of the liver; hyaline thrombi in the spleen; hemorrhagic nephritis; oophoritis	Peritoneum	Peritonitis; ulcerative lesions in the ileum	Intestinal lymphoid hyperplasia; focal necroses in the liver	+	Blood, feces, peritoneum, pericardium, necrotic areas in the ileum.
2 4½ yr.	7 days	4 days	Str. viridans	105.6	30,000 86	Peritonitis; periappendicitis; mesenteric adenitis; hemorrhagic enterocolitis; perisplenitis; bronchopneumonia	Pulmonary edema; degeneration of the liver; splenic infarct; emboli in the kidneys; mesenteric adenitis; myocarditis	Peritoneum, throat, blood, spinal fluid, feces, bone marrow	Peritonitis; pericarditis; focal hemorrhagic enterocolitis	Ulcerative and hemorrhagic lesions in the ileum and appendix; mesenteric adenitis; vascular necrosis and thrombosis; pulmonary edema; hemorrhagic pleuritis; focal necroses in the liver	+ (organism and toxin)	Blood, feces, throat, peritoneum, spleen, liver, pericardium, spinal fluid
3 3½ mo.	Noted on admission	5 days	Str. viridans	105.2	24,500 54 band forms	Peritonitis; periappendicitis; mesenteric adenitis; focal hemorrhagic lesions in the ileum and cecum; perisplenitis; perihepatitis	Pulmonary infarct; congestion of the spleen; hemorrhagic nephritis	Throat, peritoneum, blood	Peritonitis; hemorrhagic and ulcerative ileitis	Focal hemorrhagic mesenteric adenitis; necroses in the liver; splenic infarct; hemorrhagic nephritis	+	Blood, feces, peritoneum
4 2½ yr.	5 days	5 days	Str. viridans	107.8	32,400 95	Peritonitis; periappendicitis; mesenteric adenitis (no autopsy)	Periappendicitis; mesenteric adenitis	Peritoneum	Peritonitis; pericarditis; congestion of the liver and spleen	Degeneration of the liver; emboli in the kidneys	+	Blood, feces, throat, peritoneum, liver, spleen, pericardium, spinal fluid
5 8 yr.	1 day	4 days	Str. viridans	107.0	18,000 90	Peritonitis; periappendicitis with superficial ulcerative appendicitis; paralyzed ileus; arthritis (?); mesenteric adenitis (no autopsy)	.....	Appendix, ulcers, peritoneum				
6 6 mo.	4 days	3 days	Nonhemolytic streptococcus	105.8	14,000 22 band forms; 60 P.N.	Peritonitis; periappendicitis; edema of the scrotum; hydrocele; perisplenitis; perihepatitis; bronchopneumonia	Bronchopneumonia; hemorrhagic pleuritis; degeneration of the liver; congestion of the spleen; acute nephritis	Peritoneum				
7 29 yr.	9 days	4 days	Nonhemolytic streptococcus	107.0	18,400 24 band forms; 60 P.N.	Peritonitis; ulcerative colitis; congested spleen	Congestion of the liver; splenic infarct; acute hemorrhagic nephritis; myocarditis; acute metritis	Peritoneum, uterine wound				
8 34 yr.	8 days	6 days	Nonhemolytic streptococcus	105.0	47,000 83 band forms; 15 P.N.	Peritonitis; periappendicitis; splenic infarct; renal abscess; pleurisy	Pulmonary congestion; degeneration of the liver; splenic infarct; congestion of a fallopian tube	Peritoneum				

* $\frac{15,000}{85}$ refers to the total leukocyte count over the percentage of polymorphonuclears. When Schilling counts were made the percentage of band forms is stated. P. N. refers to polymorphonuclear neutrophils.

† This count was made two days before death.

Serum.—The serum was obtained by bleeding rabbits 26 and 46. These rabbits successfully withstood three large injections of the streptococcus. It seemed likely, then, that the serum of rabbit 26 contained antibodies to the organism isolated from the abdominal fluid of the patient in case 1 and that the serum of rabbit 46 similarly contained antibodies to the organism isolated from the throat of the patient in case 3. The serum of each rabbit was titrated for anticomplemental action and hemolytic power. Here, too, we found that 0.2 cc. of a 1:5 dilution of the serum contained 2 units.

Saline Solution.—Fresh solutions of 0.85 per cent sodium chloride were used for all dilutions.

TABLE 6.—*Protocol of Complement-Fixation Tests Showing Antigenic Similarity of Ten Strains of Str. Viridans Isolated in Cases 1, 2, 3 and 4*

Tube	Case	Antigen	Serum		Complement, Cc.	Saline Solution, Cc.		Sensitized Cells, Cc.		Lysis
			Rabbit	Cc.						
1	1	Abdominal fluid	26	0.2	0.2	0		0.4		0
2		0.2 cc.	46	0.2	0.2	0		0.4		++++
3		0.2 cc.	0	0	0.2	0.2		0.4		++++
4	2	Peritoneum	26	0.2	0.2	0		0.4		0
5		0.2 cc.	46	0.2	0.2	0		0.4		+++
6		0.2 cc.	0	0	0.2	0.2		0.4		++++
7	2	Throat	26	0.2	0.2	0		0.4		0
8		0.2 cc.	46	0.2	0.2	0		0.4		+++
9		0.2 cc.	0	0	0.2	0.2		0.4		++++
10	2	Heart blood	26	0.2	0.2	0		0.4		0
11		0.2 cc.	46	0.2	0.2	0		0.4		+++
12		0.2 cc.	0	0	0.2	0.2		0.4		++++
13	2	Abdominal fluid	26	0.2	0.2	0		0.4		0
14		0.2 cc.	46	0.2	0.2	0		0.4		+++
15		0.2 cc.	0	0	0.2	0.2		0.4		++++
16	2	Spinal fluid	26	0.2	0.2	0		0.4		0
17		0.2 cc.	46	0.2	0.2	0		0.4		+++
18		0.2 cc.	0	0	0.2	0.2		0.4		++++
19	3	Throat	26	0.2	0.2	0		0.4		0
20		0.2 cc.	0	0	0.2	0.2		0.4		++++
21		0.2 cc.	46	0.2	0.2	0		0.4		0
22	3	Heart blood	26	0.2	0.2	0		0.4		0
23		0.2 cc.	46	0.2	0.2	0		0.4		++++
24		0.2 cc.	0	0	0.2	0.2		0.4		++++
25	3	Abdominal fluid	26	0.2	0.2	0		0.4		0
26		0.2 cc.	46	0.2	0.2	0		0.4		++
27		0.2 cc.	0	0	0.2	0.2		0.4		++++
28	4	Abdominal fluid	26	0.2	0.2	0		0.4		0
29		0.2 cc.	46	0.2	0.2	0		0.4		+++
30		0.2 cc.	0	0	0.2	0.2		0.4		++++
31		0	46	0.2	0.2	0.2		0.4		++++
32		0	26	0.2	0.2	0.2		0.4		++++
33		0	0	0	0.2	0.4		0.4		++++
34		0	0	0	0	0.6		0.4		0

30 minutes at 37.5 C. — 15 minutes at 37.5 C.

Sensitized Cells.—The sensitizer (amboceptor) was titrated in the usual manner and was used so that at the desired dilution 0.2 cc. contained 2 units. Sheep cells washed free from the serum and packed after the final washing were used in a 5 per cent suspension. Equal volumes of the diluted sheep cells and the sensitizer were mixed. After the mixture had stood for at least half an hour it was considered suitable for use.

The antigen, complement and serum were placed in the tubes according to table 6, and the tubes were kept at 37.5 C. for half an hour. The sensitized cells were then added, and the tubes were replaced in the water bath for fifteen minutes. Throughout the test the tubes were shaken frequently. Readings were taken as soon as the test was completed and after the tubes had been in the refrigerator overnight. There was but slight variation in the two readings. Complete hemol-

ysis or lack of inhibition is represented in table 6 by ++++. Complete inhibition or lack of hemolysis is represented by 0.

The test as finally recorded shows that every strain used was able to inhibit lysis with the serum of rabbit 26. Although this rabbit was inoculated with the organism isolated from the abdominal fluid of the patient in case 1, it had antibodies which reacted with all the other strains. The uniform results with this serum showed that the various strains of Streptococcus viridans unquestionably contain a similar antigen. The possibility that the antigenic structure of the various strains is similar cannot be vouchsafed from this test alone.

The foregoing conclusion was partly confirmed by the action of the serum from rabbit 46. The definite but variable inhibition which was obtained with this serum was probably due to the absence of antibodies in any great amount. Although this serum gave complete inhibition with its own strain (tube 21), it gave only partial, and in most cases only slight, inhibition with the other strains.

This fact might argue against the identical antigenic structure of each strain, but it shows that in any case there is present in all of these organisms at least one common antigenic feature.

CORRELATION OF DATA

In all the eight patients studied there was a definite antecedent history of sore throat. The average period which elapsed between the angina and the onset of acute abdominal symptoms was five and eight-tenths days. The average duration of the disease from the time abdominal symptoms were noted until death was four and seven-tenths days. In each instance the onset was abrupt. In three cases (1, 7 and 8) the condition of the throat had cleared up prior to the development of peritonitis. In case 4 the angina improved and then recurred and was followed by peritonitis. The tendency to seasonal incidence is indicated by the fact that four of the eight reported cases occurred in a period of eight days, from March 2 to March 10. Search of the hospital records reveals only one other case of so-called primary peritonitis since 1917, and the patient in that case was admitted to the hospital on March 17, 1927. The diagnosis was confirmed at operation by Dr. A. A. Berg. There was an antecedent history of sore throat, a hemolytic streptococcus was obtained from the peritoneum, and the patient recovered.

Three adults and five children were affected. There appeared to be no essential difference in the clinical aspects of the disease in the two age groups. In the case of two of the adults the organism was nonhemolytic, but the general features were the same with both the viridans (five cases) and the nonhemolytic type (three cases). Extremely high temperatures were seen in both groups (from 107 to 107.8 F.). Vomiting was a prominent feature in four cases, but diarrhea was noted in only one (case 2), in which profuse watery stools were present throughout the period of hospitalization. Paralytic ileus occurred in two cases and epistaxis in one.

The organism recovered from the peritoneum was found elsewhere when it was sought. Thus, in case 2 the identical strain was found in

the throat, peritoneum, blood, feces, spinal fluid and bone marrow. In case 3 the organism was recovered from the throat, peritoneum and blood. It is noteworthy that acute arthritis was present in case 5, in which the causative organism was Str. viridans. Convulsions occurred in case 4, which may be significant in view of the fact that in the studies on animals the organism from the patient was recovered in the spinal fluid.

The initial leukocyte count was high, the general level being higher in the children than in the adults. The Schilling counts indicated active response of the marrow, the band forms in one instance (case 8) being 83 per cent of a total leukocyte count of 47,000. In case 1 there was a fall in the number of leukocytes from 15,000 on admission to the hospital to 8,600 two days before death.

The pathologic picture in each case was essentially that of streptococcic septicemia with profound toxic effects. Formation of multiple abscesses was not seen as in cases of staphylococcic septicemia. The disease process appeared to be too rapid and the causative organism too potent to permit of any localized formation of abscesses. The lesions were most evident in the lungs, liver, spleen, intestine, mesenteric nodes and kidneys. The histopathologic pictures in general were congestive or hemorrhagic owing to a toxic effect on the walls of the smaller vessels. Bacterial emboli were noted in the glomerular vessels in case 2. Splenic infarcts were present in three of the six cases in which a postmortem examination was carried out, and a pulmonary infarct was noted in a third case. The intestinal lesions were essentially focal, hemorrhagic, necrotic areas which were seen as dark red, slightly raised, round or oval areas with a well defined outline just beneath the mucosa. They were most numerous in the small intestine, particularly in the terminal portion of the ileum, and were generally accompanied by mesenteric adenitis. The microscopic picture was that of coagulation or liquefactive necrosis which was limited to the vascular submucosa and appeared to represent an effect on the wall of the vessel rather than an embolic phenomenon. Superficial nonhemorrhagic, necrotic and deeper ulcerative lesions were also noted in both the small and the large intestines. These intestinal lesions were clearcut in four of the six cases in which autopsy was performed. Aside from the intestine the toxic effects were most apparent in the liver, spleen, kidneys and lungs.

The studies in animals almost duplicated the general picture seen in the human patients clinically, pathologically and bacteriologically. The disease was produced with an unusual degree of constancy and did not depend on lowering the resistance of the animals, introduction of foreign bodies into the peritoneal cavity or mechanical injury. The frequency of pericardial involvement in the animals should be noted. Bacterial

embolism of the glomerular tufts seen in sections of the kidney in case 2 was also seen in rabbit 34.

Many of the clinical features noted in our studies have been described by other investigators. The antecedent angina has been stressed by Nordlund,[1] who reported a large series of cases which were analyzed chiefly from the clinical standpoint. Schwartz,[2] Lipschutz and Lowenburg,[3] Ransohoff and Greenebaum,[4] Girgensohn[5] and de la Chapelle[6] have stressed the focal infection in the throat, particularly in children, and the organism in each case reported was a hemolytic streptococcus. Davis and Rosenow[7] reported an epidemic of sore throat due to a streptococcus which resembled that caused by both the hemolytic and the viridans type. The clinical features were a sudden aggravation of symptoms after from seven to ten days with the development of septicemia. Positive blood cultures were obtained only when the lymph nodes were not involved. Peritonitis, arthritis and meningitis were some of the complications, and the organism was isolated from the throat as well as from the secondary lesions. On postmortem examination in four cases an acute serofibrinous peritonitis was revealed from which a pure culture of streptococci was obtained. In three instances acute fibrinous pleurisy was present, and the organism was present in the heart blood. One patient had acute pericarditis. The close similarity of these cases to ours as well as to the disease in animals is noteworthy.

In most of the reported cases a hemolytic streptococcus was isolated. Our group is exceptional, therefore, since in five cases there were the viridans and in three the nonhemolytic type. We would not, however, stress this point unduly, as technical difficulties may account for the strict differentiation of the alpha, beta and gamma organisms.

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1. Nordlund, U.: Ueber die sogenannte primäre kryptogenetische oder metastatisch Streptokokkenperitonitis: Akademische Abhandlung, reprinted from Ann. Acad. Sc. Fennicæ, ser. A., vol. 38, no. 1, Helsinki, 1933.

2. Schwartz, J.: Primary Streptococcus Peritonitis in Children, Surg., Gynec. & Obst. **45**:590, 1927.

3. Lipschutz, B., and Lowenburg, H.: Pneumococcic and Streptococcic Peritonitis, J. A. M. A. **86**:99 (Jan. 9) 1926.

4. Ransohoff, J. L., and Greenebaum, J. V.: Acute Hematogenous Streptococcic Peritonitis in Children, Arch. Pediat. **42**:315, 1925.

5. Girgensohn, R.: Ueber metastatische Peritonitis, Arch. f. klin. Chir. **141**: 196, 1926.

6. de la Chapelle, A.: Beitrag zur Kenntnis der sogenannten primären akuten Streptokokkenperitonitiden mit besonderer Berücksichtigung ihrer Beziehungen zur Angina tonsillaris, Arb. a. d. path. Inst. zu Helsingfors **2**:583, 1908.

7. Davis, D. J., and Rosenow, E. C.: An Epidemic of Sore Throat Due to a Peculiar Streptococcus, J. A. M. A. **58**:773 (March 16) 1912.

The early appearance of diarrhea, almost universally noted by other authors, was peculiarly absent in almost all of our cases and in Ziergold's [8] group.

Although a high incidence of positive blood cultures has been reported by a few authors, notably Duncan,[9] the general opinion is that during life the bacteremia is rather transient and positive blood cultures are most likely to be obtained early in the disease. The reason probably lies in the bactericidal power of the blood and the irregular and sparse feeding of organisms from the primary focus. Clinically this appears to be supported by the observation that in three of our cases the angina had completely cleared up before the onset of abdominal symptoms. Rabinowitz [10] reported an average interval of from three to four days between the onset of symptoms in the throat and in the abdomen.

The mortality in metastatic streptococcic peritonitis has been uniformly high. Nordlund reported survival in 5.3 per cent of the cases, death within two days after the onset of abdominal symptoms in 22.8 per cent and death within from four to seven days in 42.1 per cent. Our average period of survival was four and seven-tenths days and the mortality 100 per cent, a surprising thing in view of the fact that in no case was the organism of the hemolytic type, which is generally conceded by clinicians to be the most virulent. An isolated case of recovery, such as the one mentioned previously from our records, has been reported for the hemolytic streptococcic type by MacLennan and McNee.[11]

The experimental work on metastatic streptococcic peritonitis has been noteworthy by the lack of success in producing the disease by feeding or inoculation except when the injections were made directly into the peritoneal cavity after preliminary injury or in conjunction with some foreign necrotic material (Behrendt,[12] Wegner,[13] Pawlowsky,[14] Steinberg and Ecker [15]). We reproduced the disease consistently in most of our animals by the intravenous injection of eighteen-hour broth cultures. The ease with which we did this, even with some old cultures, suggests the possibility of a selective affinity of our strains

8. Ziergold, A. A.: Primary Peritonitis, Ann. Surg. **79**:418, 1924.

9. Duncan, J. H.: Canad. M. A. J. **24**:778 (June) 1931.

10. Rabinowitz, M. A.: Acute Hematogeneous Streptococcic Peritonitis, Am. J. M. Sc. **157**:797, 1919.

11. MacLennan, A., and McNee, J. W.: Primary Streptococcal Peritonitis in a Child with Septicemia Ending in Recovery, Brit. J. Dis. Child. **10**:258, 1913.

12. Behrendt, R. A.: Experimental Peritonitis Produced by Injection of Bacteria, Proc. Soc. Exper. Biol. & Med. **31**:543 (Feb.) 1934.

13. Wegner, G.: Arch. f. klin. Chir. **20**:51, 1876.

14. Pawlowsky, A. D.: Centralbl. f. Chir. **14**:881, 1887.

15. Steinberg, G., and Ecker, E. E.: J. Exper. Med. **46**:362, 1928.

for the intestine and peritoneum. Steinberg and Goldblatt,[16] using virulent Bacillus coli, found that intraperitoneal injection of saline suspensions produced bacteremia in dogs, but no deaths. Tragacanth suspensions, however, produced severe toxemia and death. Bolton [17] showed that colloidal dyes passed through the wall of the peritoneum and capillaries into the blood more slowly than crystalloids. Starling demonstrated a relationship between the osmotic pressure of blood proteins and the absorption of fluid by the blood vessels. By increasing the protein content of a peritoneal saline solution the absorbing power was reduced to the intracapillary hydrostatic pressure, and no further absorption occurred. He stated that in the saline suspensions the organisms rapidly pass into the blood stream and are destroyed before any great amount of toxin has been produced. David and Sparks [18] noted the protective action of a plastic peritoneal exudate in preventing the passage of diphtheria toxin from the dog's peritoneum into the blood stream.

Dandy and Rowntree [19] expressed the belief that absorption from the peritoneal cavity is usually hemic rather than lymphatic and did not support the view of the intraperitoneal flow to the diaphragm. This is of interest in connection with the metastatic pleural, pulmonary and pericardial lesions. Woolsey, however, took the opposite view and was supported by the work of Buxton and Torrey,[20] who injected lamp black and typhoid bacilli intraperitoneally and found the maximum concentrations in the liver and spleen.

Wallgren, using intraperitoneal inoculations in rabbits, found that he could produce fatal peritonitis only in susceptible animals. This method does not, of course, simulate pharyngogenic hematogenous streptococcic peritonitis in man.

PATHOGENESIS

The clinical features of the disease generally known as primary streptococcic peritonitis point to the throat as the primary source of infection in most cases in which a careful history is obtainable. We have reproduced the disease in rabbits by means of intravenous injection of strains recovered from patients with the disease. Antigenic studies

16. Steinberg, S., and Goldblatt, H.: Studies on Peritonitis, Arch. Int. Med. **39**:446 (March) 1927.

17. Bolton, C.: Absorption from the Peritoneal Cavity, J. Path. & Bact. **24**:409, 1921.

18. David, V. C., and Sparks, J. L.: The Peritoneum as Related to Peritonitis, Tr. Am. S. A. **46**:362, 1928.

19. Dandy, W. E., and Rowntree, L. G.: Peritoneal and Pleural Absorption with Reference to Postural Treatment, Ann. Surg. **59**:587, 1914.

20. Buxton, B. H., and Torrey, S. C.: Absorption from the Peritoneal Cavity, J. M. Research **10**:3, 1906.

established the similarity of strains. The pathologic lesions in both the human patients and the animal subjects were almost identical. Our bacteriologic and histopathologic studies have established the true hematogenous, metastatic, septicemic nature of the disease arising from a primary focus in the pharynx. The mechanism of peritoneal involvement may be directly through the blood stream, but we are of the opinion that it occurs through the focal hemorrhagic and ulcerative lesions in the intestine. The organisms are brought to the intestines in the blood stream and are excreted through the intestinal wall into the lumen of the intestine. We repeatedly recovered the organism in the feces after intravenous inoculation, as we had previously reported, with the bacilli of Sonne-Duval and Flexner dysentery. The intestinal lesions are produced by the streptococcic toxin. The organisms in the intestine, viable and potent, then pass out through the focal lesions into the peritoneal cavity. The absence of intestinal necrosis in some cases does not invalidate this view as the effects of toxin on the intestinal mucosa must not necessarily produce visible lesions in order to render the wall permeable. There is ample experimental evidence to support this contention. The production of visible intestinal lesions depends on the strength of the toxin, the virulence of the bacteria and the length of time during which they act; finally, many of our peritoneal cultures, both of our patients and of the rabbits, were contaminated with Bacillus coli, strongly suggestive of the intestinal origin of the streptococcus. The absence of the organism from the rabbit's intestine as shown by control studies before each animal was used and the presence of the organism in the feces after intravenous injection, accompanied by necrotic lesions in the intestinal wall and peritonitis in which both the Streptococcus and Bacillus coli were found, constitute fairly conclusive evidence of the mechanism involved in the production of pharyngogenic hematogenous streptococcic peritonitis.

NOTE.—Since this paper was submitted for publication two additional cases have been studied. The first was that of a man aged 26 who was admitted to the hospital on April 27, 1935. Death occurred fourteen days after the angina and seven days after the onset of acute abdominal symptoms. The second was that of a man aged 46, who was admitted to the hospital on May 5, 1935. Death occurred eight days after the angina and one day after the onset of acute abdominal symptoms. Str. alpha (viridans) was recovered in both cases. Postmortem examination was made. The results of the clinical, bacteriologic and pathologic examinations and the studies on animals duplicated those reported in the paper in their essential details.

CARCINOMA OF THE CERVIX UTERI

CLINICAL STUDY OF NINE HUNDRED AND FORTY CASES

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The aspects of cancer which have received most attention in the literature of recent years have been its etiology, its early diagnosis and its treatment. This is no doubt as it should be, and yet much can be learned from the analytic survey of large numbers of cases from the standpoint of the clinical symptoms presented by the patients, the age incidence and the associated physical findings. For example, the duration of bleeding before medical advice is sought should throw an interesting light on the patient's alertness or apathy to this ominous symptom and serve as a justification of the efforts being made to educate women on this point. Again, the question arises whether cancer always can be checked in an early stage even when the patient does pay prompt heed to the symptoms or whether, on the other hand, the patient may not be doomed in many cases no matter how intelligent and alert she may be.

The study of 940 cases of cervical cancer from the gynecological department of the Johns Hopkins Hospital has been undertaken from this general standpoint without any great effort to divide the patients into groups. The results, as will be seen, support my impressions on certain points, while in other respects they are somewhat unorthodox. It was scarcely to be expected that the study would reveal any outstanding sign or symptom which would materially aid in diagnosis; though medical science has advanced with great strides during the past forty years, the knowledge of cancer seemingly well illustrates Bacon's rather unkind comment on medicine in general: "Medicine is a science which has been as we have said, more professed than laboured, and yet more laboured than advanced. The labour having been in my judgement rather in a circle than in progression. For I find much iteration and small progression."

HISTORICAL BACKGROUND

Before presenting the results of this investigation it seems worth while to sketch briefly the development of the clinical knowledge of cervical cancer, if for no other reason than that my own experience has shown me how difficult it is to get the historical data in any collected form without laborious search through many often rather inaccessible sources.

From the Gynecological Department of the Johns Hopkins Hospital.

Ancient authors rarely mentioned this lesion as such, though innumerable papers are devoted to lesions of the breast and skin. The Ebers Papyrus advised that a "woman with a devouring disease of the vulva should be treated with an ointment of arsenic and vinegar," a therapeutic palliative that still is employed in one form or another. Centuries before, in India, Ramayana was advising that cancerous growths be removed with red hot irons. Celsus (30 B. C.-38 A. D.) appreciated the lumpy quality of cancer as a diagnostic aid, especially the condition of the axillary lymph glands in cancer of the breast. And one of his aphorisms has held through the centuries, viz. "only the beginning of cancer admits cure." Albucasiss expressed the same idea in his voluminous treatise on tumors, in which he noted: "When cancer has become old and large you should have nothing to do with it. I have never been able to cure it, nor have I ever seen any one who has." Charlatans flourished in those days as they do now; at this same time Pliny the Younger was advising that "carcinomatous sores are treated with hare's rennet sprinkled upon them with an equal proportion of capers in wine." However, Pliny's remedy is more rational than those employed by the many quacks of the present day. Galen (131-203 A. D.) added his pneumodynamic theory to the doctrine of a pathologic condition of the humors upheld by Hippocrates, pointing out that women of melancholic disposition were especially subject to cancer, particularly after the menopause. He added that when menstruation is regular woman is exempt from the disease. He recognized its malignancy and advocated a combined therapy of medical and surgical measures and stressed the necessity of early diagnosis. Aetius of Amida (502-573 A. D.) in the collected works of Rufus of Ephesus offered the first clear description of cervical cancer. "The tumor was usually at the cervix, hard, resistant, and even to the touch, and reddish, almost livid. From it came a thin watery reddish-yellow discharge." Paulus of Aegina (625-690 A. D.) claimed that it was possible to differentiate between chronic metritis and cancer of the uterus with the aid of a vaginal speculum devised by Archigenes. The value of this instrument was not appreciated, and its use was soon limited and later given up. In the eleventh century, Avenzoar (1070-1162) introduced the nutrient enema, and in the same century Petroncellus advocated digital exploration in the examination for cancer of the rectum and uterus.

In the sixteenth century, Daniel Sennert (1572-1637) of Prague severely criticized the views then existing about the nature and classification of cancer, and he advanced the theory of the contagiousness of cancer. He compared cancer to leprosy and elephantiasis and from this deduced its transmissibility. To support Sennert, Zacutus Lusitanus, a Jewish physician in Portugal, presented the following case: "A poor woman who had suffered many years from an ulcerated cancer of the

breast, slept at night on the same couch with her three sons, and all three became afflicted." The contagiousness of cancer is accepted by many even today, and this belief is not limited to the laity. In 1777, a Mr. Nooth inoculated himself with tissue and fluid from a cancerous growth, but the experiment failed. Copland cited an instance in which the husband developed cancer of the penis following coitus with his wife who was suffering from cervical carcinoma. In 1865, Moore suggested that cancer was a local disease and that changes elsewhere in the body or possible serologic variations were not the result of growths. He asserted, moreover, that the recurrence of cancer following operative removal is due to the fact that some of the growth has been left and that some persons are more susceptible to cancer than others. Shortly after this, Waldeyer, Cohnheim and others inaugurated the modern trend of thought, which it is scarcely necessary to review in this paper.

SYMPTOMS

Symptoms presented by the patients are listed in order of their frequency.

Complaint	Cases	Incidence, Percentage
Metrorrhagia	243	25.8
Pain in the lower quadrant of the abdomen	112	11.9
Irregular menstrual periods with spotting	72	7.6
Irregular, prolonged menstrual periods	66	7.0
Tumor; vaginal mass	49	5.2
Bleeding after coitus	45	4.8
Bleeding with foul discharge	38	4.0
Foul bloody discharge	37	3.9
Odorless discharge	35	3.7
Irregular periods with foul discharge	25	2.6
Irregular periods with bloody discharge	24	2.5
Odorless bloody discharge	24	2.5
Irregular periods with odorless discharge	21	2.2
Weakness with bleeding	21	2.2
Urinary symptoms with bleeding	20	2.1
Urinary symptoms; no bleeding	14	1.5
Lower quadrant pain and backache	14	1.5
Irritating odorless discharge	11	1.2
Foul discharge	10	1.0
Piles; rupture; change of life	9	0.9
Dysmenorrhea	8	0.9
Back pains	7	0.7
Arthritis; joint pains	6	0.6
Tumors with discharge	4	0.4
Chills; fever	3	0.3
Urinary symptoms with bleeding and discharge	3	0.3
Headaches	3	0.3

Bleeding.—Vaginal bleeding in one form or another leads the duality of cardinal symptoms, bleeding and discharge, occurring in 620 cases (65 per cent). Metrorrhagia was present in 243 cases (25.8 per cent), without noticeable leukorrheal discharge being present. However, every gynecologist knows that many patients deny the presence of a discharge or "whites" and that in not a few of them moderate or even profuse vaginal discharge is found on examination. Thus the value of designating this group of cases as characterized by bleeding alone is questionable.

Few women who come to the public clinics keep careful records of their menstrual cycle, so that the 138 cases (14. 6 per cent) represent only those in which I felt certain there was a definite upset in menstrual rhythm. Increased frequency of the menstrual period is the most common change, but a few women stated they experienced periods of amenorrhea; in one instance it was of eight months' duration in a patient 33 years of age. The age of the patients rules out most possible menopausal changes, as all of them were under the age of 40.

Postcoital Bleeding.—Spotting after intercourse occurred in only 45 patients (4.8 per cent). This is a surprisingly small percentage. In many of the early cases there is sufficient change in the surface epithelium to explain the occurrence of bleeding following trauma. The basal layer loses its normal protective strength, and thus the capillaries are exposed; the delicate network of papillary outgrowths readily break, and the slightest touch will result in a venous ooze.

Duration of Bleeding.—The average length of time that bleeding persists is approximately six months. The maximum period of bleeding with scant leukorrheal discharge was thirteen years. When this patient was examined, she was found to have an operable growth. The condition of another patient, a 26 year old colored multipara, was diagnosed as being marked cervical infection. Cauterization was advised, but the patient refused to have it done. One year later she returned to the clinic, and carcinoma with parametrial invasion was found on examination. Spotting after intercourse was present in another patient following a subtotal hysterectomy two years before; she complained of dyspareunia. At the time of operation the cervix had been treated conservatively, but no microscopic study had been made.

The severity of the hemorrhage does not, in all cases, indicate the extent of the disease, nor does the length of time the patient has had the condition necessarily suggest that the case is hopeless. Patients with profuse intermenstrual bleeding and profuse periods have been operated on successfully, while the condition of many without any apparent bleeding has been diagnosed as "hopeless."

Vaginal Discharge.—Usually associated to some extent with bleeding, vaginal discharge was present in 20.6 per cent of the cases. Half of the patients denied the presence of a noticeable odor. No bacterial studies on these patients were made, but the studies made by Philipp [1] support my belief that control of the bacterial infections will not only

1. (*a*) Philipp, E.: Zur Virulenzfrage der Streptokokken, Klin. Wchnschr. **2**:1925 (Oct. 15) 1923; (*b*) Virulenz Bestimmung von Blutkeimen, München. med. Wchnschr. **70**:493 (April 20) 1923; (*c*) Statistik der Karzinome des Collum uteri und der vagina aus den Jahren 1923-1925, mit kritischen Bemerkungen zur Therapie, Strahlentherapie **43**:102, 1932.

alter the type of discharge but in most instances alleviate much of the pain. The value of bacteriologic studies of the cervix in this condition is doubtful because of the varied flora always present in the vagina.

Pain.—Limited to the lower abdominal quadrants, pain was present in 112 cases (11.9 per cent). In half of these the pelvic examination suggested a secondary adnexal inflammatory process. Backache associated with lower abdominal pain was present in 14 cases (1.5 per cent). In no case with the growth localized in the cervix and with no involvement of the adnexa and broad ligaments was pain present. The pains are so varied in type that it is not possible to use them as a diagnostic aid. The cervix is peculiarly insensitive to pain, and the pain is not experienced until the process has invaded the parametrium. Invasion of the rectum and the bladder produces symptoms characteristic of the site, while lateral invasion may exert pressure on the nerve trunks, with resultant symptoms in the lower extremities.

Though the presence of pain in most instances does signify invasion of an ineradicable tumor, there are many patients with secondary infections who often present pains of a more severe type than would be expected from the stage of the disease. Pain should not limit the examination, nor should it necessarily serve as a guide for treatment.

Urinary Symptoms.—Four hundred and seventy-three (50.3 per cent) of the patients gave a history of irritation of the urinary tract, and the records on the majority of the patients are thorough enough to rule out previous infections of this tract. Fourteen (1.5 per cent) patients visited the clinic because of urinary complaints alone, while 3 (3 per cent) had symptoms suggesting pyelitis and had been treated before admission because of renal infection. The following table lists the urinary symptoms in the order of their incidence:

Complaint	Cases	Incidence, Percentage
Nocturia (3 or more times)	192	20.0
Nocturia; frequency	70	7.4
Nocturia; dysuria	49	5.2
Dysuria	45	4.8
Dribbling; incontinence	41	4.3
Burning	28	3.0
Burning; nocturia	26	2.7
Burning; frequency	21	2.2
Burning; frequency; nocturia	18	1.9
Dysuria; nocturia, frequency	18	1.9
Frequency	13	1.4
Hematuria; nocturia	13	1.4
Dysuria; burning; frequency; nocturia	13	1.4
Frequency; dysuria	10	1.0
Urgency	7	0.7
Hematuria	4	0.4

It is known that any one, or all, of these symptoms may arise from irritation of any portion of the urinary tract and that their presence calls for an effort to locate their origin.

The following case is significant.

A white woman, aged 23, was recently admitted to the medical service with the diagnosis of uremia; she had been vomiting for two weeks and gave a history of spotting following coitus for two years. Although she had been under medical supervision by her private physician over this period and had made known her vaginal bleeding to him on numerous occasions, no pelvic examination was ever made. She had had three normal pregnancies, with a history of edema of the extremities following the last. Pelvic examination revealed a large necrotic cauliflower-like mass filling the vaginal vault, with extensive involvement of the broad ligaments. An endeavor was made to catheterize the kidneys to relieve the renal suppression, but marked obstruction of the ureteral lumen made this impossible. The course was rapidly downward, and the patient died a typical "uremic death" several days after admission.

Faerber [2] found that in 88 (58.7 per cent) of 150 patients dying of carcinoma of the cervix there was definite evidence of disease of the bladder. He listed the incidence of urinary lesions found as follows: simple cystitis, 11; cystitis hemorrhagica and exulcerans, 13; cystitis gangraenosa, 26; tumor metastases, 8; direct invasion of the tumor, 9; and suppurating cavities, 10. In 84 cases (56 per cent) there was definite ureteral involvement and in 108 cases (72 per cent) the kidneys showed damage. It is also very interesting to note that there was bilateral hydronephrosis in 55 cases and unilateral hydronephrosis in 40; pyonephrosis in 20 and pyelitis and pyelonephritis in 19. Warren [3] in his series noted that renal involvement was the cause of death of one third of his patients. Williams found definite hydronephrosis in over 85 per cent of his 78 postmortem studies on patients with cervical carcinoma and demonstrated renal damage in every case. Kraul [4] in Peham's clinic found pyelitis or pyelonephritis in 85 per cent of the cases and uremia as the cause of death in 50 per cent. His postmortem studies revealed that the damage to the kidneys resulting from hydronephrosis was secondary to ureteral obstruction.

The postmortem studies in this series are few, because most of the patients with a so-called hopeless condition are either transferred to the city hospitals or sent home; however, postmortem studies on 24 patients showed definite involvement of the urinary tract in 65 per cent. According to Band and Wade,[5] death from cervical cancer is usually due to the three following complications: (1) renal infection, either from an ascending or from a blood-borne pyelonephritis; (2) renal suppression,

2. Faerber, H.: Woran sterben die nicht operierten bzu. Rezidiv gewordenen Uterus Karzinomkranken? Ztschr. f. Geburtsh. u. Gynäk. **99**:213, 1931.

3. Warren, Shields: The Grading of Carcinoma of the Cervix as Checked at Autopsy, Arch. Path. **12**:783 (Nov.) 1931.

4. Kraul, L.: Zentralbl. f. Gynäk. **47**:1573, 1923.

5. Band, D., and Wade, H.: Vesical Exclusion in Treatment of Carcinoma of Cervix Uteri, Tr. Edinburgh Obst. Soc., 1930, p. 89.

usually from ureteral obstruction, and (3) toxemia from septic absorption. The same authors recognized six definite stages of involvement of the bladder from anterior extension of the tumor: (1) elevation of the bladder floor; (2) fixation of the bladder floor; (3) circulatory changes, as recognized by congestion or petechial hemorrhages; (4) formation of a transverse ridge; (5 and 6) malignant invasion, displaying its presence in the form of an ulceration, of hypertrophic nodules or of a vesicovaginal fistula.

The presence of an extrinsic tumor mass pushing against the bladder is easily overlooked in the early stages, unless there is some change in the outline of the normal vesical floor with visible congestion. It is very likely that early irritation of the base of the bladder results in a variety of urinary symptoms, even when there are no findings from cystoscopic examination. The edema resulting from a compromised lymphatic circulation in most cases precedes the tumor mass and presents two definite stages. The lymphatics in the wall of the bladder are the first to be involved, the walls becoming edematous and presenting a glazed appearance. The second stage follows closely and is characterized by an irregular edema of the mucosa, the so-called bullous edema. It is during the latter stage that the tumor mass may be visible, especially in those areas less affected by the edema. The fixation of the bladder in the absence of infection denotes definite involvement of the wall and often produces a transverse ridge. Finally the wall of the bladder is penetrated, gross hematuria results, and the formation of a fistula occurs in time. Microscopic hematuria may result from vesical congestion secondary to lymphatic stasis.

Ureteral involvement does not necessarily keep pace with the vesical changes, and it is possible to have one without the other, though not for long. Periureteral infiltration by the carcinoma, with its concomitant inflammatory reaction, occurs without recognizable changes in the bladder and produces, in order, hydro-ureter, hydronephrosis and uremia, as the occlusion of the ureters advances. The proximity of the cervix to the ureterovesical area makes it practically impossible for the malignant process to reach any advanced stage without involving the ureters; however, it is well known that the ureteral wall is peculiarly resistant to the invasion of cancer and that the occlusion is the result of pressure. If the tumor extends into the parametrium, treatment by irradiation occasionally results in ureteral damage, though the number of such instances are surprisingly few. With the appearance of the ureteral symptoms, the value of irradiation is diminished, as the destructive action of radium may include the renal tract. Many patients seemingly cured by irradiation and enjoying good health for years suddenly succumb to damage of the renal tract. Some physicians even advocate the

implantation of ureters in those patients suspected of having suffered ureteral damage. However, I feel that so radical a procedure as ureteral transplantation should never be resorted to except under most unusual conditions. In most instances ureteral drainage can be secured by proper measures applied before and after the therapy for carcinoma.

The appearance of urinary symptoms in patients known to have cervical carcinoma is sufficient indication for a thorough examination of the urinary tract before exposing the patient to either surgical or radiologic procedure. The presence of hematuria in such patients commands at least a study of the bladder, while a vesicovaginal fistula in an untreated patient is usually indicative of a far advanced stage, but many steps can be instituted to make such a patient comfortable. Comfort for the patient presupposes a knowledge of the degree of involvement of the urinary tract. Sufficient drainage will make the final days of the patient with a so-called hopeless case less painful and easier to control with sedatives. In reviewing these urologic conditions in this series it was depressing indeed to note the number of patients who had received oral medication for their symptoms, without any form of physical examination, before coming to the clinic.

Constipation.—This condition occurred in various degrees of obstinacy in many of the patients and often was associated with hemorrhoids, but in the entire series only 5 histories suggested rectal involvement before the formation of a fistula. The first rectal symptom is often a proctitis, usually associated with a foul vaginal discharge and is invariably relieved when the type of discharge changes. The patients in this series were not sufficiently explicit on this point, and thus the conclusions are based on very few cases. Following the congestion of the rectal mucosa a varying degree of rigidity appears, slowly forming in some cases a scarlike retraction and narrowing of the lumen. Constipation becomes more pronounced and is followed by tenesmus. The rectal mucosa becomes edematous and on examination presents a smooth glassy appearance. The vaginal discharge finally may assume a fecal odor as the last stage with ulceration, and penetration of the rectal mucosa occurs.

Loss of Weight.—Loss of weight, as listed by the numerous observers of patients in the gynecological department over a period of forty years, receives varying degrees of accent. Fifteen per cent of the histories make no mention of weight, and one may presume that the patient had not lost sufficient weight to attract her attention. Thirty-three per cent gave either no known loss of weight or a possible slight gain in weight; thus 52 per cent of the series showed definite change in weight. In the histories "some loss" is considered as being from 5 to 10 pounds (from 2.3 to 4.5 Kg.); "moderate to marked," from 20

to 30 pounds (from 9.1 to 13.6 Kg.). The average loss of weight for the 52 per cent of the patients is approximately 15 pounds (6.8 Kg.), with a loss of 65 pounds (29.5 Kg.) over a period of six months as the maximum. Twelve patients sought medical aid primarily because of the loss of weight.

Recently a 33 year old colored nullipara, complaining of loss of weight, increasing weakness and scant spotting following coitus and douches, sought assistance in the clinic because her "clothes no longer fitted her." She had lost 44 pounds (20 Kg.) over a period of six months but was able to continue as a cook in a large club. Examination revealed a large, firm, smooth mass totally obliterating the landmarks of the cervix and extending into the parametrium. There was no tenderness, but the Schiller test was decidedly positive and a biopsy confirmed the results of the test. Following irradiation she had a foul discharge, with cramplike pains in the lower quadrants of the abdomen and frequency of and burning on urination. Opiates were necessary to alleviate the pain. The patient had been examined elsewhere several times during the previous two years because of postcoital spotting, and each time palliation was advised.

The loss of weight does not vary proportionally with the hemoglobin content or the degree of malignant invasion. Although it is commonly present in late stages of the disease, its presence does not serve as a diagnostic aid. However, loss of weight in a woman warrants not only the usual tests and examinations to rule out the possibility of cardiorespiratory lesions but a pelvic examination to rule out the possibility of cancer.

Anemia.—The lowest hemoglobin content in our series was 12 per cent, this being in a 36 year old colored multipara who had "moderate" vaginal bleeding for three months, accompanied with foul discharge. On examination the growth seemed localized, and a successful total hysterectomy was performed. Following several transfusions she was discharged from the service with a hemoglobin content of 48 per cent. Four years later she had a hemoglobin content of 95 per cent with no suggestion of recurrence. Another patient had been bleeding for approximately the same length of time; on examination her hemoglobin content was 87 per cent. A subtotal hysterectomy had been done four years before, and she was treated with radium, without success. A woman complaining of loss of weight (25 pounds, 11.3 Kg.) and vaginal bleeding with foul discharge had a hemoglobin content of 95 per cent. The growth, however, had already invaded the parametrium.

The average hemoglobin count of this series of patients was 72 per cent, with the minimum 12 per cent and the maximum 105 per cent. This average is equal to that of a group of young women taken at random and higher than that of a group of an equal number of nurses

working in an institution. Although the estimation of the hemoglobin content does not serve as a diagnostic factor, it is an aid in the medical treatment of the patients with inoperable cancer.

RÔLE OF PREGNANCY

The predisposing rôle of pregnancy and labor in the causation of cancer is generally accepted. However, no convincing evidence has been offered to prove that pregnancy possesses either a retarding or a stimulating effect on a malignant growth. Since over 90 per cent of all cases of cervical cancer are said to occur in women with a history of parturition, the appearance of the tumor during the puerperium should not be surprising; indeed, in view of the frequency of cervical carcinoma, it is surprising that its appearance at this time is not more common.

One hundred and three patients (10.9 per cent) of the present series stated that they had never been pregnant; the veracity of the patient is rarely questioned, though it is not a rarity to have a patient admit falsification at a later date. In 13 per cent of the series there was a history of only 1 pregnancy. These figures agree with those of most observers, though Frankl found 3 per cent nulliparas in his series; Johnson and Tyrone [6] reported 3.4 per cent in 926 patients. Frigyesi,[7] in his series of 690 patients, reported 74 per cent multiparous, 12 per cent nulliparous and 14 per cent primiparous. Other observers reporting nulliparas in their series include Martzloff with 5.4 per cent, Kauffmann with 10.1 per cent, Graves with 9.2 per cent and Bartlett and Smith [8] with 10.7 per cent. Mattmüller found 9.7 per cent of the patients to be nulliparas and felt justified in reporting 10 in his series of 440 patients as virgins.

With 10 per cent as an acceptable average figure I call attention to Hinselmann's study [9] of the Prussian statistics in which he found that 10 per cent of the female population over the age of 35 were unmarried. The nuptial knot does not purport pregnancy, nor does celibacy connote virginity, but in a large series the nonconformists of one group probably offset those of the other. Thus statistically speaking, one might say that cervical carcinoma is not influenced by pregnancy.

In the 837 women (89.1 per cent) of the present group with histories of pregnancy, there was an average of 5.16 pregnancies per patient or

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6. Johnson, C. G., and Tyrone, C. H.: Uterine Cancer; Report Covering Period June 1927 to June 1932, Surg., Gynec. & Obst. **58**:113 (Jan.) 1934.

7 Frigyesi, J: Oruoskepzes **20**:178, 1930.

8. Bartlett, M. K., and Smith, G. S.: Carcinoma of the Cervix; Study of Cases Treated at the Free Hospital for Women Between 1875 and 1929, Surg., Gynec. & Obst. **52**:249 (Feb.) 1931.

9. Hinselmann, H.: Ueber die Prophylaxe des Portiokarzinoms nach Bossi-Spirito, Zentralbl. f. Gynäk. **55**:3362, 1931.

a total of 4,319. The average for the entire series is 4.6 pregnancies. In England, Lever found that the patients had an average of 5.75 children in his series of 103 cases; this figure is above the average for England, but we cannot assume that frequent parturition causes cancer. In this series I have included known abortions, miscarriages, surgical interventions and spontaneous deliveries. It is of interest that I found three white women with 21 children apiece, while the maximum for the colored group was 14 children.

Stöckl,[10] reviewing 18,000 deliveries in Posen, found only 8 cases of cervical carcinoma (0.04 per cent). There was no evidence in his series to suggest that the growth of cancer is influenced in any way by pregnancy. Experiments by von Graf and Maude Sly on animals suggest that pregnancy does not hasten the growth. However, various observers hold there is an accelerating influence and offer several theories to account for this influence, i. e., hyperemia of the pelvic tissue, disappearance of certain hypothetic protective substances from the blood stream and various changes in the blood, such as an increase in the hypophyseal hormone, as suggested by Hofbauer and others.

Mayer found 18 patients with cancer (1.6 per cent) in a series of 1,106 pregnant women; O'Malley and Walsh stated that it occurs once in each 2,000 deliveries. From the reports in the literature one may conclude that the percentages range from 0.04 per cent to 1.8 per cent with the average below 1 per cent. The rarity of its occurrence does not justify its being disregarded, and cancer must always be considered a possibility in the gravida. Too frequently is bleeding during the puerperium hastily passed by on the assumption that it is an insignificant accompaniment of pregnancy. Profuse bleeding in the pregnant woman is often diagnosed as placenta praevia. It is more difficult to determine the presence of early carcinoma in a pregnant woman than in a non-pregnant woman, but a careful examination of the exposed cervix is indicated in every instance of bleeding. According to Phillip, pregnancy does not affect the treatment, and the early finding of the growth may make it possible to deliver a living child and to cure the mother.

Keller [11] reported the case of a 38 year old multipara with a history of bleeding for three weeks, ante partum; no vaginal examination was made. She was delivered spontaneously at home and three weeks later sought advice for a persistent vaginal hemorrhage. An advanced carcinoma was found. One of the patients in the present series was a 28 year old multipara, with no abnormal prenatal symptoms, who was delivered spontaneously at home. One month later a scant spotting after coitus

10. Stöckl, E.: Kollumkarzinom und Schwangerschaft, Ztschr. f. Geburtsh. u. Gynäk. **101**:437, 1932.

11. Keller, R.: Au sujet du dépistage du cancer du col pendant la grossesse, Bull. Soc. d'obst. et de gynéc. **21**:77 (Jan.) 1932.

appeared, followed shortly by a malodorous discharge. Six weeks after parturition on examination a carcinoma was found. A successful total hysterectomy was performed, and she was free from recurrence ten years later. Another patient, a 37 year old multipara, was delivered spontaneously; her antepartum history is unreliable. Two months after delivery she noticed a scant postcoital spotting. Three months later a thin, foul discharge appeared, and she sought relief. Cancer was found and a total hysterectomy was performed, followed by irradiation. The patient died three months after the operation. The duration of the symptoms and the lapse of time before most patients seek medical attention vary greatly. Proper antepartum and postpartum examination of these women would have permitted an early diagnosis.

Accepting chronic infection as a paramount factor in the etiology of cervical cancer, parturition is the most important cause of these "irritation areas." According to most observers, malignant conditions rarely develop in or near the site of injury but occur on the margin of the subsequent erosions and eversions. The studies of Hinselmann,[9] Bonney, Hunner and Bartlett and Smith [8] have demonstrated well the paucity of malignant conditions in cervices treated conservatively, and Pemberton in a recent study of 5,962 cervices which had been either cauterized or repaired reported only 5 carcinomas. Thus the eradication of the unhealthy cervical tissue and the repair of the lacerations resulting from delivery will remove the primordium of cervical cancer.

AGE AND RACE INCIDENCE

In the minds of most of the women who come to a public clinic, the age of the menopause is viewed with dread, for it is with this normal physiologic epoch that cancer has been associated since the days of Galen. Many an otherwise normal person is started on the road of chronic neuroticism because of this unfounded fear, enhanced by hearsay and information gleaned from the notices of patent medicines. Carcinoma is no respecter of age, and in this regard the results of the present series agree with those of most observers. In the following table the incidence of corporeal cancer in a large group of patients is noted for comparison:

Age Groups	Patients with Cervical Cancer	Percentage	Patients with Corporeal Cancer	Percentage
20-24	18	1.9	..	....
25-29	60	6.4	4	2.4
30-34	88	9.4	1	0.6
35-39	146	15.5	11	6.8
40-44	162	17.2	18	11.1
45-49	149	15.8	28	17.2
50-54	124	13.2	48	29.6
55-59	80	8.5	28	17.2
60-64	57	6.2	14	8.6
65-69	30	3.2	5	3.1
70	26	2.7	5	3.1
	940		162	

There is 1 case of corporeal cancer to 5.8 cases of cancer of the cervix. Sixty-six and three tenths per cent of the cervical growths in the patients of the present series occurred before the age of 50 years, while 61.7 per cent of the corporeal growths appeared after this period. The average age for the patients with cervical cancer is 46.1 years; for the patients with corporeal cancer it is 52.8 years. Seventeen and seven tenths per cent of the cervical lesions occur in patients before the age of 35, with 8.3 per cent appearing before the thirtieth year.

There is a gradually increasing literature on cervical cancer in extreme youth. Bumm [12] reported an adenocarcinoma in a 7 month old child; this was confirmed histologically by Aschheim, and Scheffey and Crawford [13] reported the same lesion in a child at the age of 22 months.

On the other hand, it is of interest that Donald and Shaw [14] in their series of 177 patients with cancer of the body reported only 1 under the age of 40 years. In the present series there are 16 patients under the age of 40, with 4 under the age of 30 years. Kehrer and Neumann [15] reported the lesion in a 15 month old child, and Taussig [16] presented the case of a 10 year old girl with carcinoma of the body.

The authenticity of many of these cases in extreme youth is doubtful, for the proximity of the wolffian duct opens a possible site of origin for "mixed tumors" of congenital type. Before such cases can be regarded as authentic a thorough histologic examination by more than one accepted authority should be required. In this series, the youngest patient was 20 years old and the oldest was 79.

Without doubt age is a salient factor in cancer of the uterus, but the age incidence must be made to include the early twenties. The appearance of either bleeding or vaginal discharge, regardless of the age of the patient, indicates that an examination of the cervix is advisable.

Over a period of forty years the patients whose cases have been recorded in the gynecological clinic are about evenly divided between the white and the colored races. In this series of 940 patients, 470 (50 per cent) belong to the colored race; thus there seems to be no racial

12. Bumm, E.: Karzinomatöses Uterus eines sieben Monate alten Kindes, Deutsche med. Wchnschr. **35**:1331, 1909.

13. Scheffey, L. C., and Crawford, B. L.: Adenocarcinoma of the Cervix in a 22 Months Old Child, Am. J. Obst. & Gynec. **24**:118 (July) 1932.

14. Donald, A., and Shaw, W. F.: Age Incidence of Carcinoma of the Body of the Uterus, Proc. Roy. Soc. Med. **22**:19 (Jan.) 1929.

15. Kehrer, E., and Neumann, H. O.: Uteruskarzinomexstirpation bei einem 1¼ jährigen Kind, Monatschr. f. Geburtsh. u. Gynäk. **81**:68 (Jan.) 1929.

16. Taussig, F. J.: Questionable Uterine Cancers in Very Young Persons, S. Clin. North America **5**:1437 (Oct.) 1925.

preference of the malignant condition. Fifty-six per cent of the cases of corporeal cancer occurred in the white race.

HEREDITY

The patient with cancer cares little whether he is a victim to an inherited susceptibility, to a malformation of tissues or to cancer itself; to the clinician and to the person without cancer, the factor of heredity is of paramount importance. One hundred and thirty-two (14 per cent) of the patients in the present series stated that one or more of their blood relatives had died of "cancer." To serve as a norm, 500 successive medical histories were studied, and an occurrence of 11.5 per cent were found. The value of these observations is doubtful, for it is evident that an accurate genealogic history is not easily obtained. There is no evidence in this series to suggest that either cancer or the predisposition to cancer is hereditary. The fact that several members in successive generations have died of cancer is certainly not proof that the trait, be it a recessive or a dominant character, is passed on in the germ cell. Hutchinson [17] found that in less than 6 per cent of 50,000 cases of death from cancer was there a history of familial malignant disease. Waaler [18] has recently studied the familial histories of 6,000 patients with cancer and found himself confronted with so many extrinsic factors that satisfactory deductions were difficult. He stated the belief, however, that hereditary susceptibility plays a part, as in his series cancer was more frequent among blood relatives. One must not overlook the possibility that these persons are more frequently exposed to the same "cancer-producing" agent.

The paucity of acceptable data on heredity makes it impossible to evolve any valuable conclusions, for it would be necessary to have dependable statistics on several generations. At the present time there is no adequate evidence for assuming that some persons are predisposed to cancer.

CANCER IN THE CERVICAL STUMP

In presenting the cases of cancer occurring in the cervical stump after subtotal hysterectomy, we do not intend to enter into a debate as to the efficacy of total hysterectomy over the subtotal operation. Twenty-two (2.3 per cent) cases in our series occurred in the cervical stump, including 1 case of adenocarcinoma. Johnson and Tyrone [6] found 21 cases in their series of 926 patients; 10 of these had received previous cervical treatment. The lapse of time following the subtotal

17. Hutchinson, Woods: Preventable Disease, New York, Houghton Mifflin Company, 1909.

18. Waaler, G. H. M.: Ueber die Erblichkeit des Krebs, Oslo, Jacob Dybwad, 1931.

operation and the appearance of the malignant condition in this series showed fourteen years as the maximum and one year as the minimum, with an average of five years. With six months as the average duration of symptoms in this series, I believe it possible to classify these cases into two groups. If the growth appears after a period of two years it is considered a new growth; with this rule the percentage of carcinoma in the stump is reduced to less than 0.2 per cent. This low percentage can be further reduced if, during the surgical removal of the uterus, the cervix is either cauterized or repaired as indicated.

SUMMARY

The importance of early diagnosis has been appreciated for more than 3,000 years and, except for the advent of the microscope, little change has taken place in the present methods of diagnosis.

In this series of 940 cases the average age was 46.1 years, with cancer occurring in 66.3 per cent before the age of 50 years. The patients were evenly divided between the two races, and over 10 per cent stated that they had never been pregnant.

Bleeding from the vagina, in one form or other, is the most frequent factor in bringing the patient to seek medical aid. The duration of bleeding averages six months. Postcoital spotting occurs in less than 5 per cent.

Involvement of the urinary tract was present in 50 per cent of the cases, with nocturia the most frequent complaint.

Pregnancy apparently does have some influence on the growth of the tumor, and the commonly attending laceration of the cervix is a cardinal factor in producing chronic irritation.

The average hemoglobin content is 72 per cent, which is no lower than that of normal women doing institutional work.

Loss of weight has no diagnostic value, as the average loss was only 15 pounds (6.8 Kg.), and 50 per cent of the patients did not report any change in weight.

The possible influence of heredity is still a disputed question.

Pain is present in such a variety of pelvic lesions that it is of no diagnostic aid; rarely, if ever, does it appear with cervical cancer before parametrial invasion, but it may be seen in even early cases combined with other pelvic lesions.

Twenty-two cases occurred in the cervical stump following subtotal hysterectomy, with an average lapse of five years. The growth may be assumed to have been preexistent if it occurs within two years after the operation. The incidence of cancer of the stump in this series is less than 0.2 per cent.

Rectal invasion is rare except in advanced cases, but it is probably more frequent than is suspected.

Loss of weight, amount of bleeding, type or severity of pain, age, heredity and number or frequency of pregnancies do not govern necessarily either the malignancy or the degree of invasion in carcinoma of the cervix. The complaints are so manifold that the appearance of a patient, regardless of her complaints, warrants a thorough examination, which is not complete without a speculum exposure of the cervix

A REVIEW OF UROLOGIC SURGERY

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(*Concluded from page 344*)

URETER

Occlusion.—Bugbee [33] reported that he had performed nephrectomy, following irradiation of the uterine cervix for carcinoma, in 6 cases at the Woman's Hospital since 1930. In the past year, 2 other cases were seen; in one there was occlusion of both ureters, and in the other unilateral occlusion; in both instances, the occlusion was secondary to irradiation of the uterus. All except 1 of the patients in Bugbee's series of cases complained of bleeding from the vagina; all but 1 revealed a squamous cell carcinoma of the cervix at biopsy. All except the last were treated at the Woman's Hospital, with radium, one or more tubes being inserted into the cervical canal for a minimal dosage of 1,787.5 mg. hrs. and a maximal dosage of 4,857.68 mg. hrs. In 3 cases, needles were also inserted into the cervix, and 5 patients received treatment with roentgen rays of high voltage. In 4 cases, the carcinoma had extended to the wall of the vagina. None of the patients revealed evidence of metastasis when first treated, or had symptoms which were referable to the urinary tract at the time of the first irradiation. The urine was normal in all but 1 case. The obstruction of the ureter was unilateral in 7 cases and bilateral in 1 case; the average distance of the obstruction from the ureteral orifice was 4 cm., and in 3 cases there was a uretero-

33. Bugbee, H. G.: Ureteral Occlusion Following Radium Implantation into the Cervix, Tr. Am. A. Genito-Urin. Surgeons **27**:329, 1934.

vaginal fistula distal to this point of obstruction. In the first 6 cases, a functionless kidney, the condition of which was the result of pyonephrosis secondary to ureteral occlusion, was removed. The time which had elapsed between the irradiation and the nephrectomy in these cases was as follows: twenty-two months, seven months, five months, seven months, twenty-two months and nine years, respectively.

Deane described three reactions to radiation, in terms of surface reaction: The first was an irritation, which occurred within twenty-four hours; the second was an erythema, which appeared at the end of a month and was the result of a temporary localized vasomotor paralysis, a condition which may progress to destruction of tissue; the third, which formerly was called a delayed radium burn, was a specific radiation change and was the result of an obliterative endarteritis. The cases of vesical injury that he reported were of the third type and appeared in a minimum of ten months after irradiation.

Trauma.—Sisk [34] stated that a large number of operations have been described for the repair of operative injuries of the ureter, but all are based on the principles of end-to-end, end-in-end or side-to-side anastomoses. The technic used by Sisk combines the principles of simplicity, splinting of the ureter, maintenance of caliber and satisfactory drainage. It is the procedure of choice for the repair of ureters thus traumatized, with certain exceptions which will be mentioned later. The technic is as follows: A ureteral catheter, as large as will move freely through the ureter without interfering with the circulation, is introduced into the ureter and passed into the pelvis of the kidney. Introduction may be made through a cystoscope or the catheter may be passed each way from the point of injury, the lower end being brought out through the urethra later. Over this catheter, end-to-end anastomsis is performed, the sutures of fine catgut being passed through the serous and muscular layers of the ureter. With satisfactory drainage, the catheter may be left in place for many days to prevent contraction of the lumen during healing.

Variations of this procedure are necessary in cases in which the injury is sufficiently low to permit reimplantation into the bladder, which is preferable; or when a segment which has been removed is of sufficient length to cause tension. If there is tension, satisfactory healing will not occur and implantation into the intestine is the operation of choice. Cases in which there are old injuries must be considered as separate entities. After appropriate examinations to determine the condition of the kidneys and ureters, a satisfactory procedure must be selected. This may be a plastic repair, implantation into the bladder or intestine, nephrostomy or nephrectomy.

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34. Sisk, I. R.: Operative Injuries of the Ureter, Tr. Am. A. Genito-Urin. Surgeons **27**:287, 1934.

Ectopic Outlet.—Deming [35] reported that ectopic ureters opening into the vagina produce uniform symptoms of vaginal dripping of urine, together with normal urination. The opening of an ectopic ureter into the vagina is on the anterior wall of the vagina, near the midline, and anywhere from the hymen to the uterine cervix. A supernumerary ectopic ureter opening into the vagina always runs to the upper pole of the kidney. The right side is more frequently involved than the left. The kidney attached to the ectopic ureter is of small functional value and is prone to infection. No attempt should be made to conserve such a ureter and kidney. Heminephrectomy may be done if the vessels to each kidney are distinct. Once the kidney is infected, nephrectomy is indicated. Total ureterectomy is a satisfactory method of treatment when infection is not present.

Empyema.—Smith [36] reported a case in which the right ureter terminated superiorly in a fibrous insertion in the peritoneum. In this fibrous termination, a few tubules were found. The lower end emptied into the bladder in an anomalous situation; the entire pelvic portion of the ureter was dilated and full of pus. It had produced partial obstruction to the emptying of the bladder by pressure on the trigon from behind, and the infection had caused a toxemia. The entire ureter was removed, and the defect in the right lateral wall of the bladder was closed with a continuous suture of catgut. The neck of the bladder admitted the tip of the finger readily. A tube was left in the bladder, a cigaret wick was inserted in the prevesical space, and a rubber drain was placed in the right iliac fossa, behind the peritoneum.

Regurgitation.—Vermooten and Neuswanger [37] said that complete excision or incision of the ureterovesical valve of a dog will always result in incompetence, as shown by regurgitation up the ureter of contents of the bladder. Regurgitation of uninfected or infected urine up a normal ureter will not cause dilatation of the ureter. Ureteral dilatation will be caused by regurgitation up an infected ureter. Ascending infection does not necessarily occur when infected contents of the bladder regurgitate up a normal ureter. Ureteral infection may occur as the result of ulceration of the epithelium of the ureter. This infection may progress by direct extension upward and downward in the loose areolar tissue of the tunica propria of the mucosa, without the aid of the lymphatics. If this infection extends beneath the epithelium of the

35. Deming, C. L.: Ectopic Vaginal Ureter, Tr. Am. A. Genito-Urin. Surgeons **27**:297, 1934.

36. Smith, G. G.: Empyema of the Ureter Associated with Aplasia of the Kidney, Tr. Am. A. Genito-Urin. Surgeons **27**:321, 1934.

37. Vermooten, V., and Neuswanger, C. H.: Effects on the Upper Urinary Tract in Dogs of an Incompetent Uretero-Vesical Valve, J. Urol. **32**:330 (Oct.) 1934.

mucosa which lines the pelvis and calices of the kidney, pyelitis results. The ureteritis in these intsances usually is limited entirely to the tunica propria and does not ordinarily extend to the ureteral musculature. Periureteric inflammation was not observed in any of these experiments.

Anastomosis.—Zollinger [38] said that previous experimental evidence indicates that better results can be obtained in uretero-intestinal anastomosis if the ureter is temporarily protected from contamination. Open lymphatics of the ureter that become contaminated at the time of operation probably are a major route of ascending infection of the kidney.

A mechanical appliance is described which fulfils the experimental requirements for protection of the ureter and which permits the immediate aseptic drainage of urine. The mechanical efficiency of the drainage button which is described can be improved markedly by changing the design to allow the parts to screw together, thus preventing their separation. It is suggested that a drainage button of the same design as the present one, but much larger, could be used advantageously.

Ureterostomy.—Fresnais [39] said that only a few cases in which ureterostomy had been performed had been recorded up to 1920. In 1921, iliac implantation of the ureter was described by Legueu and Papin. Since that time, Papin, Marion and Rosenkranz have employed cutaneous ureterostomy in cases in which exclusion of the bladder was necessary after nephrectomy for tuberculosis, but Thevenot in 1924, and Lepoutre in 1926, still maintained that, owing to the rarity of cases in which this operation had been employed, its value could not yet be estimated.

If important disturbances of the bladder appear after nephrectomy for tuberculosis, examination must first establish the cause of these troubles. If they arise from stones or inflammation of the bladder, the condition may be treated as if the patient did not have tuberculosis. If, on the other hand, the inflammation is of a tuberculous nature, the primary focus of infection must be determined, and the possibility of a vesico-ureteral reflux must be considered.

A cyst in the bladder which reappears indicates a tuberculous kidney, and in such cases the walls of the ureter generally are hardened. If the cyst, however, has persisted even after nephrectomy, the tuberculous infection may come from the ureter of the side which has been subjected to operation, and the remaining kidney may not be involved. The infection also may arise from the bladder itself. The infection in the bladder has proved tenacious in most cases.

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38. Zollinger, Robert: Uretero-Intestinal Anastomoses: The Use of Mechanical Anastomosing Apparatus, Surg., Gynec. & Obst. **59**:796 (Nov.) 1934.

39. Fresnais, Jean: L'urétérostomie cutanée dans le traitement des cystites rebelles chez les néphrectomisées pour tuberculose, J. d'urol. **38**:315 (Oct.) 1934.

The reflux to the remaining kidney has been studied only recently by means of roentgenography. The roentgenogram reveals the point at which the ureter enters the bladder, and shows whether the reflux is confined to the ureter or whether it mounts to the renal pelvis; sometimes the ureter is dilated; sometimes it is flexuose or kinked. The bladder may be normal, or it may have shrunk in size. The reflux causes pain and frequent or irregular urination, because of the diminished size of the bladder. The major importance of the reflux lies, however, in its tendency to infect the remaining kidney. The intensity of pain and the existence of reflux are the two factors which determine exclusion of the bladder. By ureterostomy, therefore, the patients may be relieved and the remaining kidney saved from contamination.

Cutaneous ureterostomy has the advantage over intestinal ureterostomy in being less hazardous, although in some cases the latter has given excellent results (Papin, 1925). It is, however, too risky in cases in which a single kidney remains.

The advantage of ureterostomy over cystostomy is evident. The latter does not prevent reflux and hence does not exclude contamination of the kidney, or does it entirely relieve the patient. In several cases on record, cystostomy had to be followed ultimately by ureterostomy.

With nephrostomy, the reflux is entirely prevented and pain is relieved, but this procedure does not completely exclude the bladder unless the ureter is tied or even severed. Nephrostomy injures the renal parenchyma and reacts on the anatomic status of the kidney. It also promotes serious infection by reason of the catheter. The necessity of inserting the catheter in the back is, furthermore, a great inconvenience to the patient. The argument that after nephrostomy the normal course of the urine may be reestablished after a certain time of detoxication does not hold in view of the fact that complete assurance of exclusion of the bladder is given only if the ureter is put out of commission. Nephrostomy is, therefore, in effect as final as ureterostomy.

Ureterostomy is contraindicated if the ureter is too narrow, or if the kidney itself is infected. In the latter case, nephrostomy is always preferable because it allows better drainage of pus pockets than does ureterostomy.

The technic of ureterostomy is now confined to iliac implantation. A sufficiently long portion of the ureter must be isolated to permit easy conduction to the skin. After implantation, a Nélaton catheter is inserted as far as the renal pelvis, in order to prevent retention. The catheter is changed from time to time. After healing, only a short catheter is left in place, and the patient can attend to this. A rubber pocket serves to receive the urine, which in nearly all cases will be discharged drop by drop.

The results of ureterostomy are satisfactory and permanent, all patients having been immediately relieved. The influence of the operation on the ureter can only be called beneficial, no dilatation or loss of tone having been observed. The roentgenogram revealed dilatation of the renal pelvis and calices, but this was most likely the result of the reflux which was present before the operation.

The only objection to ureterostomy lies in the possibility of an ascending infection; this has been observed frequently, but only rarely has it been of an extremely serious nature. As infection after nephrostomy is just as likely, the possibility of infection after ureterostomy seems to offer no decisive argument against its practice.

BLADDER

Tumors.—Spooner [40] reported that of 163 definite cases of tumor of the bladder in which necropsy was performed, metastases were found in 49 (29 per cent). Of the patients who had metastatic lesions, 65 per cent were considered as amenable to surgical treatment; many had the possibility of surgical cure as far as could be determined clinically. The most frequent site of malignant extension is the regional lymph nodes; they were involved in 34 (69 per cent) of the 49 cases. Lymph nodes represented the only apparent site of metastasis in 12 (24.4 per cent) of the cases. Metastatic growths were found in one or more distant viscera in 24 (48.9 per cent) of the cases. The liver was involved in 14 of these cases and the lung in 9. Skeletal involvement is not an ordinary finding in metastasis of tumor of the bladder. Estimation of the incidence of metastases, based on many surgical studies, may be inaccurate because exploration for metastases was not made. Clinical data presumably indicative of extravesical extension are often obtained by rectal examination, by elicitation of a long history, by determination of a large lesion cystoscopically, by disclosure of a lesion by biopsy, by a malignancy which is graded 3 or 4 and by the presence of persistent pain which is unexplained by the local lesion. Of the 163 cases in this series, 29 per cent presented metastatic lesions. In many of these cases, metastasis had not been suspected at the time of the clinical examination.

Quinby,[41] in discussing carcinoma of the urinary bladder, has established certain standards in regard to the suitability of a patient for total cystectomy. Among these is an involvement of the floor of the bladder so wide that if the carcinoma were to be treated locally by any method, such treatment would involve the outlet of the bladder to such an extent that loss of vesical function and incontinence would result. There should

40. Spooner, A. D.: Metastasis in Epithelioma of the Urinary Bladder, Tr. Am. A. Genito-Urin. Surgeons **27**:81, 1934.

41. Quinby, W. C., in discussion of Spooner,[40] p. 92.

be no demonstrable metastasis outside the bladder; in each case, before performing a total cystectomy, he has investigated the retroperitoneal drainage area from the bladder. Frequently, he has been disappointed by finding involvement of the preaortic lymph nodes or of the lymphatic channels leading from the pelvis to that region. The patient is further studied by ordinary roentgenography or by whatever other methods are available to demonstrate secondary deposits. In those instances in which the peritoneum is opened and the retroperitoneal regions are investigated, they are often found to be the site of secondary deposits. It may be possible to treat these regions in a manner similar to that used in treating the axilla in carcinoma of the breast, namely, by dissection, but this is a matter for the future. If it is possible to make a comprehensive dissection of these regions, some benefit may result.

Caulk [42] said that he was studying some 500 cases of neoplasms of the bladder with reference to the upper urinary tract. The study of 300 cases had been completed with reference to the renal involvement, and it was found that the kidney may be involved in three ways: (1) by simple regurgitation from incompetency of the ureteral valve, which is disturbed by the spread of the tumor as it invades the mucous membrane; (2) by stenosis of the ureter, and (3) by extravesical occlusion of the ureter from involvement of the lymph nodes or as a result of superimposed inflammatory reactions around them. In cases in which there was a possibility of invasion because the tumors were situated sufficiently close to the ureter to invade it and to damage the kidney, cystographic studies revealed regurgitation in 24 per cent; in 50 per cent of these cases there was regurgitation without indentures of the wall of the bladder, and in the other 50 per cent there was invasion of the wall. Seventy-eight per cent of the tumors were situated in the region of the trigon, close to the orifices of the ureters. One hundred and forty-four patients were studied with reference to their renal functional capacity as indicated by nitrogenous studies of the blood or by excretory tests, particularly by the phenolsulphonphthalein test. Of these 144 patients, 44 per cent showed definite diminution of renal function; 21 per cent of the 300 patients revealed renal infection. There were 90 deaths. In 38 per cent of the cases in which death occurred, there was positive evidence of disease of the upper urinary tract. Twenty-five of these cases came to necropsy; in 60 per cent of these cases, death had been caused by renal disease, a large renal mortality.

Carcinoma of other organs may extend to the bladder. In 400 cases of carcinoma of the cervix uteri, extension to the bladder occurred in

42. Caulk, J. R., in discussion of Spooner,[40] p. 93.

3 per cent, and death occurred as a result of renal disease in 50 per cent of these. Whether the tumor is primarily vesical or secondary to extension, the kidney is likely to suffer. The only way to protect the kidney in these cases is by early diagnosis and prompt treatment. In this series of cases, two years and eight months elapsed between the initial symptom and the special study. This condition is improving under medical education.

Weijtlandt [43] reported a case of primary endometriosis of the bladder or adenomyosis vesicalis interna which occurred independently of, and was in no way connected with, an endometriosis of the uterus or adenomyosis uteri interna which was also present. Of the 26 cases of endometriosis of the bladder which have been reported, only 3 belong to the autochthonous or primary variety.

Cases of endometriosis may be divided into two groups: In the first group, there is a direct connection between the normal endometrium and the dystopic endometrial tissue. In the second group, the tumor develops without any direct connection with the mucosa of the uterus. The growths are found in the ovary, round ligament, pouch of Douglas, rectum, cecum, ileum, umbilicus and bladder, and on the serosa of the fallopian tubes and uterus.

Weijtlandt's patient was 31 years of age. She had had profuse menorrhagia since she was 15 years of age. This had not responded to treatment, which had included cuneiform excisions from both ovaries. Her uterus and right ovary, which was cystic, were removed eleven years later. Section of the uterus showed a typical endometriosis which did not extend through the walls or involve the serosa.

However, six weeks after operation new symptoms developed. These consisted of hematuria and painful and frequent urination, which recurred at regular intervals for about three weeks, with an intermission of one week. Cystoscopic examination revealed bullous edema, which extended between the ureteral orifices, just above the interureteric ridge, and at the posterior lip of the vesical outlet. There were several vesicles with blue centers, which looked as if they were filled with blood. A diagnosis of primary endometriosis of the bladder was made, because the endometriosis of the uterus did not even extend through the muscularis and the intervening serosa over the uterus, and the bladder was not involved at the time of operation.

Operation was refused; therefore, roentgenologic castration was attempted to remove the influence of the remainder of the left ovary on the endometrial tissue. This was successful in checking the hemorrhage from the bladder, at first, but there were relapses, and later roentgenologic treatments did not have any effect.

During an appendectomy, attempts were made to remove the remainder of the left ovary, but the excised tissue disclosed only fibrous tissue. Finally, under sacral anesthesia, the endometrioid tissue in the wall of the bladder was fulgurated three times at intervals of ten days. Although enough time has not elapsed to determine whether a permanent cure will be brought about, the result to date has been entirely satisfactory.

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43. Weijtlandt, J. A.: Endometriosis of the Bladder, Proc. Roy. Soc. Med. **27**:1493 (Sept.) 1934.

In most of the cases which have been reported, the diagnosis has been made after operation and histologic examination. The clinical symptoms and signs which should insure recognition are indicated in the following summary:

(*a*) Endometriosis of the bladder can be diagnosed only during the period of menstrual activity, not before the beginning of menstruation and not after the menopause.

(*b*) The disturbances are periodical, coinciding with the menstrual cycle.

(*c*) In the menstrual period there is frequent painful micturition, and the urine contains albumin and blood. In the intermenstrual period there are no, or only slight, subjective symptoms.

(*d*) Bimanual vaginal examination may detect a soft swelling, which is tender during menstruation.

(*e*) Cystoscopy reveals the true nature of the condition. There is swelling of part of the mucous membrane of the posterior wall of the bladder. This locality is explained by the position of the uterus in the case of endometriosis of that organ, and by the mesodermal origin of the trigon, and by the ureteric orifices in the case of autochthonous endometriosis of the bladder.

The treatment of endometriosis of the bladder differs according to the age of the patient. In women who are near the menopause, castration by means of roentgen rays is the simplest method. In women who are young, the most efficient treatment is radical excision of a segment of the bladder. This should always be performed by laparotomy, in order that one may be informed of the relations of the vesical endometriosis to the internal sexual organs and to the peritoneum. If this operation, for any reason, is not feasible, intravesical electrocoagulation may be tried.

Tuberculosis.—Thomas, Kinsella and Van Winkle [44] expressed the opinion that the first treatment prescribed in cases of tuberculosis of the bladder should be complete rest in bed, just as in the treatment of other active lesions of tuberculosis. For several years they have used light bipolar diathermy to control tuberculous lesions of the bladder. This was first brought to their attention in endeavoring to control hemorrhage in a tuberculous bladder. The ulcer, or the portion of the bladder which was bleeding, was thoroughly coagulated with bipolar diathermy, by using a weak current with low amperage. Care was taken to produce a superficial destruction of the inflamed, ulcerated area. This treatment

44. Thomas, G. J.; Kinsella, T. J., and Van Winkle, Charlotte C.: Treatment of Tuberculosis of the Urinary Bladder, Tr. Am. A. Genito-Urin. Surgeons **27**:55, 1934.

not only controlled the bleeding but afforded the patient relief from urinary frequency and from burning and pain at urination. The patient soon requested that this treatment be repeated, because some of the bleeding had recurred and because urination was less painful following treatment than it had been before. This time, in addition to cauterizing the bleeding areas, every inflamed region in the mucosa of the bladder was coagulated. Three or four subsequent treatments were administered. The capacity of the bladder increased, the urinary frequency decreased, and the distress during urination was eliminated.

Subsequently this method of treatment had been used in a large number of cases in which ulcers of the bladder did not respond to the ordinary hygienic methods of treatment. Almost complete relief of the vesical symptoms was obtained in each case, particularly when it was possible to remove the lesion in the kidney, which might continuously reinfect the bladder. Treatment for tuberculosis of the bladder was administered to several patients who had had a nephrectomy but had tuberculosis in the remaining kidney. Rest in bed, plus light coagulation of the inflammatory areas in the bladder, alleviated the symptoms; in some instances, the lesions healed completely. When the patient is a man, the urologist must definitely ascertain that there is no coexisting tuberculosis of the prostate or prostatic urethra. Infection in these structures may prolong the urinary frequency and painful urination, and result in ulcerations in the bladder.

When ulcers of the bladder are treated with bipolar diathermy, spinal anesthesia is advisable. Care should be taken to see that the treatment is always under the direction of the eye. The electrode is not moved around the bladder recklessly. Its end must be in sight at all times before the current is turned on, so that the depth of the coagulation may be carefully controlled. Examination of sections of a bladder that has been treated by diathermy suggests that the cautery tip should not be in contact with the mucosa of the bladder more than a second in any one place. The length of each treatment is limited, so that all the ulcerated areas are not treated at one session. A subsequent treatment should not be given earlier than fourteen days after the previous one. This method of treating tuberculosis of the urinary bladder has, in their experience, given more relief than any other method.

Thomas, Kinsella and Van Winkle [45] suggested certain changes in the usual cystoscopic technic in examinations for genito-urinary tuberculosis. They advised: the use of an anesthesia that will permit painless cystoscopy, with minimal trauma; thorough disinfection of all instruments; proper sterilization of ureteral catheters, and employment of a

45. Thomas, G. J.; Kinsella, T. J., and Van Winkle, Charlotte G.: Cystoscopic Technic Necessary for the Diagnosis of Genito-Urinary Tuberculosis, Tr. Am. A. Genito-Urin. Surgeons **27**:65, 1934.

careful aseptic technic throughout the cystoscopic examination. A detailed inspection of the prostatic urethra is necessary. Some method should be devised to prevent contamination of ureteral catheters during their passage to the renal pelvis. The amount of ureteral reflux should be determined, and large specimens of ureteral urine should be obtained for inoculation of guinea-pigs. The proper evaluation of differential functional tests with sodium indigotindisulphonate U. S. P. or other dyes is important. Bilateral pyelograms should be made, unless there is some contraindication. These should be inspected immediately, and other pyelograms should be made if the first ones are unsatisfactory. Repeated urologic study is necessary before a complete diagnosis is made and before radical treatment is undertaken.

Atony.—Braasch and Thompson [46] said that atony of the bladder is never primary; it is caused by abnormal innervation, by obstruction or by both factors. For the purpose of clinical differentiation, atony resulting from disease affecting the innervation may be regarded as primary. Continuous retention of urine from any cause will produce atony of the wall of the bladder. In some cases it may be difficult to determine which factor is involved. In most cases of atony, obstruction, either primary or secondary, is the predominating factor. The factors which cause sphincteric dysfunction are: imbalance of innervation, with predominance of the sympathetic or filling nerves; rigidity or failure of adequate relaxation of the internal sphincter, which is known as dysectasia, and apparent failure of coordination of the reflexes involved in the act of urination, centering in the neck of the bladder, called achalasia. The first condition can be favorably influenced by presacral neurectomy, and the second condition usually can be remedied by thorough transurethral resection. Knowledge concerning cases in which other causes are operative is insufficient as a basis from which to determine treatment, but in a case of this type which they observed, presacral resection restored function to normal.

The abnormal tissue which interferes with function of the neck of the bladder may in some cases be easily overlooked. It is necessary to remove such tissues completely and to free every cicatricial contraction in order to restore function of the sphincter. Sphincteric abnormality in the female presents problems markedly different from those in corresponding conditions in the male. In most cases, judicious removal of sphincteric tissue will overcome retention, but subsequent presacral neurectomy may be necessary. Localized or partial atony may follow destruction of branches of the nerves of the pelvis in the course of an operation which involves the bladder. Various other types of atony may occur.

46. Braasch, W. F., and Thompson, G. J.: Treatment of the Atonic Bladder, Tr. Am. A. Genito-Urin. Surgeons **27**:99, 1934.

In the presence of acute retention, such as frequently occurs following abdominal operation, the advisability of drainage of the bladder before it becomes overdistended should be emphasized. In contrast, in the presence of retention following extensive injury to the spinal column, overflow of the bladder should be permitted rather than to catheterize the patient. It is evident that much remains to be discovered in the mechanism of urination, and concerning the various lesions which may affect it.

Ulcer.—Pollak [47] reported 2 cases of simple ulcer of the bladder. Several known factors and the favorable influence of pregnancy suggest that the menstrual cycle is a causative factor in the development and continuation of these ulcers. Local disturbances of the blood supply may also be of importance in producing these simple ulcers or in causing them to recur. Occasionally, a loosely adhering incrustation also may be found attached to the ulcer. Methylthionine chloride U. S. P. (methylene blue) applied locally has been the most successful of the conservative means of local treatment. A study is being made to determine the mode of action of this drug in the treatment of ulcer of the bladder. Of the more radical methods of treatment, fulguration of the ulcer gives the best results.

Fibrosis.—Crenshaw [48] reported the late results of panmural fibrosis (Hunner's ulcer) of the bladder. The apparent rarity of this condition was soon discovered to be the result of failure of recognition, and many cases have since been reported. It is not always easy or possible, at the first cystoscopic examination, and in the presence of concurrent cystitis, to distinguish panmural fibrosis from chronic pyogenic areal cystitis; with treatment of the infectious lesions by irrigation, the masking cystitis usually is relieved and pyuria disappears, leaving the cystoscopic picture and persistent symptoms of panmural fibrosis. The symptoms often are so typical that a diagnosis can be made from them alone. These symptoms are: marked urinary frequency, with gradually decreasing capacity and increasing irritability; constant pain, which can often be localized to one area in the bladder and which is markedly increased by a distended bladder; frequent hematuria with distention of the bladder; complete or nearly complete absence of pus in the urine, in contrast with the extreme irritability of the bladder and usually negative culture of the urine.

At present at the Mayo Clinic one type of treatment after another is tried, with overdistention probably giving the best temporary results.

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47. Pollak, Walther: Ueber das Ulcus simplex der Blase, Ztschr. f. urol. Chir. **39**:362, 1934.

48. Crenshaw, J. L.: Late Results in Panmural Fibrosis of the Bladder, Tr. Am. A. Genito-Urin. Surgeons **27**:109, 1934.

Satisfactory overdistention can be performed only with the patient under an anesthetic, and should be done only under observation through a cystoscope, so that the overdistention can be terminated immediately if tears appear in the mucous membrane. Fulguration gives rapid relief from pain, but the pain soon recurs. Following fulguration, as with excision of the lesion, there is often a larger recurrence or multiple recurrences in other parts of the bladder.

Of 123 patients who had panmural fibrosis, 5 were men and 118 were women. Of the women, 93 were married and 25 were single. Forty-five of 47 patients who were treated for this lesion, and who are still living, were females and 2 were males. At the time of the first symptoms, the oldest patient was 61 years of age, and the youngest, 14 years; the average age was 37.4 years. The maximal duration of symptoms when the patient was first admitted for observation was thirty years, and the minimal, three months, and the average was six and six-tenths years.

Treatment of the bladder is not now being taken by 41 patients; regular treatment is being taken by 4, and 2 are taking an occasional irrigation. Temporary improvement occurred in 35 cases, but was absent in 2 cases. Judging from the value for the blood urea or from the excretion of phenolsulphonphthalein, from the results of roentgenologic examination and from the presence of renal pain or renal symptoms, renal disease was not present in any case when the patient was first seen at the clinic.

In evaluating the final results in these cases, Crenshaw considered the patient's statement, as well as the present symptoms and findings, such as frequency, capacity of the bladder, hematuria, pain and general health. Of the 47 patients, 19 were improved greatly or cured; 9 were improved considerably; 6 were improved slightly or moderately. The condition was stationary in 10 cases and worse in 3. In other words, after from five to twenty years, 34 patients were cured or improved, and the condition of 13 was stationary or worse than it was before the treatment was administered.

PROSTATE

Electroresection.—Cabot [49] said that in recent developments of transurethral resection of the prostate, two types of technic have been used: one may be called the Young-Caulk-Bumpus type; the other, the Stern-Davis-McCarthy type. The former method depends on cutting away portions of the prostate with a circular knife introduced through the sheath, the bleeding being controlled by touching the bleeding points under sight. This involves a minimum of coagulation of tissue. The

49. Cabot, Hugh: The Battle of the Prostates, Surg., Gynec. & Obst. **59**:682 (Oct.) 1934.

second method depends on the removal of tissue by means of a wire loop charged with a high frequency current. Bleeding is further controlled by direct coagulation. In the first of the two types there is relatively little coagulation, and consequently not as much danger of deep necrosis, which may later be followed by secondary hemorrhage when the slough separates. In the second method, particularly when performed by a less skilled surgeon, relatively large amounts of coagulation may occur, causing the death of a considerable amount of tissue, which is not removed.

These operations have been extensively employed during the last year. The Stern-Davis-McCarthy method has been selected by the majority of operators because the instruments are similar to the cystoscopes commonly used. The Young-Caulk-Bumpus method utilizes instruments with which few even trained urologists are familiar.

The occurrence of accidents in transurethral resection of the prostate emphasizes the necessity of graduate training, even for those who are already expert in the field of urology, and the procedure should not be attempted by others. All the knowledge and experience which have proved essential to successful prostatectomy by other methods are required in the performance of this operation. Technical dexterity in transurethral instrumentation alone will not insure against the complications referred to, nor will it avoid the danger of operating on a patient who is insufficiently prepared. Cabot [49] was of the opinion that the success of this operation will depend on sound training in the surgery of the bladder, on supervised training in the technic of the methods of operation and on a sufficiently large experience to enable the operator to become thoroughly familiar with the technic. Satisfactory results will be obtained only when the operation is performed by qualified experts.

Cabot [50] said that the trend of opinion among the older generation of prostatectomists does not do justice to transurethral resection of the prostate gland. The criteria on which successful prostatectomy should be judged are low operative risk, short confinement in the hospital, complete emptying of the bladder, freedom from lasting infection and permanence of the result. Some of the difficulties in regard to transurethral resection are the result of lack of experience with the operation. A few of the recent reports on this type of operation have been based on a total experience of a small number of cases, an insufficient total to warrant any definite general conclusions.

The case for the transurethral method is strengthened if it is limited to patients operated on by surgeons of equal experience with both types of procedure. Bleeding and infection, the complications reported

50. Cabot, Hugh, in discussion of Thompson.[51]

in transurethral resection, are those with which prostatectomy of other types has been associated for forty years.

If one limits the discussion to the degree to which the two procedures meet the requirements previously mentioned for successful prostatectomy and to those cases in which the operation is done by experienced surgeons, the results seem to be as follows: The risk and the duration of confinement are less with the transurethral method, and the certainty of complete emptying of the bladder will be found better than with prostatectomy. Although it is commonly believed that all patients whose prostates have been removed "above the bone" empty their bladders completely, such is not the case. A number of patients after prostatectomy have persistent residual urine from which serious and continuous infection results. Tags of mucous membrane, scar tissue which results in bars, and large, stiff-walled cavities are not rare after prostatectomy. In recent years, persistent suprapubic sinuses have become relatively uncommon, but before that they were not rare and indicated failure to remove the obstruction completely. Complete closure of the neck of the bladder after prostatectomy has occurred many times in Cabot's experience. The results of examination of a series of patients two months or so after prostatectomy compare unfavorably with the conditions that obtain after transurethral resection of the gland. The fact that large prostates, particularly in cases in which the enlargement is of the pedunculated type of subcervical lobe, can only with difficulty be managed by the transurethral approach is not an argument against the operation. The experience is sufficient to show that for the average benign obstructing prostate the transurethral approach is the method of choice. The procedure requires special skill and training; it is Cabot's belief that it is an operation which can be satisfactorily done only by the specialist. Patients who have disease of the prostate rarely present any emergency other than the temporary emptying of the bladder. The patient is entitled to the benefits of lower risk and shorter confinement, and the support of prostatectomy because it can be done by the general surgeon is not in the interest of the patient.

Thompson [51] reported that during the four years from Jan. 1, 1930, to Jan. 1, 1934, 37 patients who had dysfunction of the neck of the bladder following prostatectomy were relieved of their symptoms by transurethral resection of the prostate gland. The type of prostatectomy did not appear to be important, for proportionately as many total failures and recurrences followed perineal dissection as followed supra-

51. Thompson, G. J.: The Value of Transurethral Resection in Relief of Dysfunction Following Prostatectomy, Proc. Staff Meet., Mayo Clin. **9**:546 (Sept. 12) 1934.

pubic enucleation. In a few cases in which the former operation had been performed, urine leaked through multiple fistulas in the perineum instead of through one above the pubic bone. From these data, prostatectomy sometimes resulted in failures other than early postoperative fatality. The mortality of transurethral resection is about a tenth that of prostatectomy. At the Mayo Clinic there was completed a consecutive series of 510 resections in 451 cases, before the next death occurred. In competent hands, incontinence seldom occurs following transurethral resection of the prostate. Cicatricial deformity with resulting contracture following operation that is done with the knife punch is rare. The incidence of recurrence of urinary obstruction because of appearance of adenomatous tissue subsequent to transurethral resection has been only a fraction of the immediate mortality from prostatectomy. Such facts indicate the value of the former procedure.

Kretschmer[52] reported 2 cases in which there were intravesical explosions, which resulted in rupture of the bladder, during transurethral electric resections. In both cases, there was a very small amount of bleeding, and the fragments of the resected prostate were aspirated with the Bigelow evacuator. After aspiration, a few tags were removed with the resectoscope, and it was at this time that the explosion occurred. Kretschmer expressed the opinion that air mixed with the hydrogen that developed during resection, and that this caused an inflammable mixture of gases. One tear was intraperitoneal and one was extraperitoneal. Both of the tears were recognized at once. They were repaired suprapubically, and the patients recovered.

[COMPILER'S NOTE.—Cases of rupture of the bladder also have been reported in the course of fulguration for tumors of the bladder. Cassuto, while fulgurating a median lobe of the prostate with a McCarthy urethroscope, noted a sudden violent explosion inside the bladder. As the bladder did not seem to be ruptured, he waited, ready to operate if peritoneal or other symptoms became alarming. A cystoscopic examination performed on the eighth day disclosed a slightly edematous bladder with large stellate cuts on its surface. Cassuto believed that the gas which accumulated from the carbonization of the tissues exploded. St. Cene, who reported 2 analogous cases, found that the explosion took place on fulguration near the upper surfaces of the bladder, where gas accumulates. In other cases, the bladder has been ruptured without fulguration. The vesical wall frequently is weakened in certain regions as the result of infection, tumors or distention. Most operators while resecting prostatic tissue remove the working element of the instrument following each bite of the loop. This permits an evacuation of the

52. Kretschmer, H. L.: Intravesical Explosions as a Complication of Transurethral Electro-Resection, J. A. M. A. **103**:1144 (Oct. 13) 1934.

water in the bladder and also permits the gas which has been generated during that single procedure to be evacuated. If the working element is left in place while several sections are being removed, gas accumulates and the distention with water is much greater. Under sacral anesthesia, overdistention of the bladder from gas or water causes the patient pain, which usually results in relief of the overdistention. Under spinal anesthesia, hazardous overdistention is more likely to occur than with sacral anesthesia. Rupture of the bladder is as much of a surgical emergency as is an acute condition in the abdomen, and delay in operating is as dangerous. It is interesting to note that in most cases in which operation has been done at once, rupture of the bladder has not had undesirable sequelae. Twenty or thirty years ago, almost all cases of rupture of the bladder, regardless of cause, proved fatal. In 1887, Ullman reported only 22 recoveries in 237 cases. In 94 of these cases, the ruptures were extraperitoneal; in 20, the patients recovered. Only 2 of 142 patients who had intraperitoneal rupture recovered. Bartels reported a mortality of 96 per cent in 98 cases in which the condition was treated without operation. Dobrowolskaja and Wiedemann reported 16 cases in which 6 patients were operated on within twenty-four hours from the time of injury; 1 patient (16 per cent) died; the other 10 were operated on in from forty-eight to one hundred and twenty hours after injury; 90 per cent of these died. In 228 (45 per cent) of the 504 cases which were reported by Packmayr, the patients died.]

Calculi.—Young [53] classified calculi of the prostate as endogenous and exogenous. The endogenous calculi are those which form within the substance of the prostate, and the exogenous calculi are found in the prostatic urethra; they have developed there in pockets or diverticula, or have reached the urethra from the kidney, ureter or bladder. Young [53] reported 100 cases. In most of these, the calculi were of the endogenous type. These cases may also be divided into those in which adenomatous hypertrophy of the prostate is present and those in which it is not.

A history of gonorrhea was noted in 36 cases (54 per cent) in which calculi of the prostate were associated with prostatitis. In the majority of cases, symptoms of the involvement of the prostate had developed soon after the incidence of the gonorrheal infection, and in many cases these symptoms had continued for years. It generally was impossible to distinguish between the symptoms that were produced by the prostatitis and those that were produced by the calculi. In many instances, the calculi were not recognized, and the patient was treated for a long

53. Young, H. H.: Prostatic Calculi, J. Urol. **32**:660 (Dec.) 1934.

time for chronic prostatitis, without improvement. The diagnosis of calculi in the prostate usually was made by roentgenography. In only a small proportion of cases were isolated calculi palpable, or was their presence detected by crepitus when pressure was made on the prostate with the finger.

The treatment employed by Young [53] in his cases varied. If the symptoms were negligible, if the prostatic secretion and the urine were sterile, and if the sexual powers were normal, operative treatment usually was not advised and no local therapy was employed. Many of these patients are rather comfortable although their prostates are filled with small calculi. In other cases in which there were pronounced local symptoms, such as irritation, burning, pain, hematuria, difficulty and frequency of urination, marked obstructive symptoms, the effects of back pressure, and pain, operative removal of the calculi was advised.

In 23 cases, adenomatous lobes or hypertrophy of the prostate was present. On rectal examination in cases in which there was prostatic hypertrophy, the calculi were sometimes felt, but the posterior layer of normal tissue of the prostate and the elasticity of the hypertrophied lobes usually made recognition of the calculi by rectal palpation impossible.

Calculi of the prostate frequently produce an induration in the prostate, which is practically identical with that felt in cases of carcinoma. This may lead to an incorrect diagnosis. In discussing diagnostic differentiation of calculi of the prostate from carcinoma of the prostate, Young [53] stressed the value of exposing the prostate by the perineal route, carefully examining it by palpation, making an incision in the suspicious area, removing a section for diagnosis and preparing frozen stained sections, if necessary.

In the cases in which there was a stone in the prostate, calculi were present in the kidney and ureter in 17 instances, and in the bladder, in 6 instances. Certain authors have observed a tendency to formation of calculi in other organs when stones were present in the prostate. Young's statistics do not confirm this assertion, although chemical examination has shown that the same ingredients that are present in calculi of the urinary tract are present in prostatic calculi. Calculi which escape from the prostate into the bladder undoubtedly may form the nucleus of calculi of the bladder, and stones which have come down from the kidney, ureter or bladder and lodge within the prostate may form calculi of considerable size within the prostate.

The exogenous type of calculi in the prostate are rare, and only a few instances of this type are to be found in the records of the Brady Urological Institute. These stones probably do not form within the substance of the prostate. The etiology is perhaps similar to that of calculi of the bladder in the presence of infection. Detritus or bacteria

may form the nuclei of these stones. Exogenous calculi are not true calculi of the prostate.

In 45 per cent of the cases in which calculi of the prostate were associated with benign hypertrophy of the gland, there was a history of gonorrhea. Fifty-four per cent of the patients without benign hypertrophy also gave a history of gonorrhea. In 50 per cent of the total number of cases, there was evidence of chronic prostatitis. In 5 cases, calculi formed within a large abscess cavity in the prostate. Infection undoubtedly is important in the etiology of stones in the prostate. In each of 44 operative specimens studied, localized infection of the prostatic ducts or prostatic acini in the region of the calcification was found. Calculi may form in prostatic ducts or in acini which are blocked with bacterial or epithelial débris. The bacterial and epithelial débris ultimately may form the nuclei of the stones. Corpora amylacea, which commonly are seen in the prostatic acini in the presence of prostatitis, possibly may act as nuclei for calculi.

Imperfect drainage of the prostate, which is caused by contracture of the orifice of the bladder or stricture of the urethra, may inhibit the discharge of secretion and pus from the prostate and, in the presence of infection, may lead to the formation of calculi in that organ. Strictures of the urethra were present in 17 per cent of the cases in which there were benign adenomas and in 13.4 per cent of the cases in which benign adenomas were absent. In many cases, these were not real strictures, but there was urethral narrowing produced by calculi. Obstructions producing retention at the orifice of the bladder were present in 17 per cent of the cases in which there were benign adenomas, and in 18 per cent of the cases in which benign adenomas were absent. Many of these were inflammatory contractures or bars.

Malignant Tumors.—Dickson and Hill [54] reported the following case:

A patient, aged 30 years, was well until four months prior to his admission to the hospital for symptoms which led to a diagnosis of tumor in the lower cervical portion of the spinal cord.

His first symptoms had been pain and stiffness in the lower part of the back. This had been followed by weakness of the upper and lower extremities and by anesthesia over the lower part of the abdomen. Spastic paraplegia had followed. This had been associated with paradoxical overflow from the bladder, retention of feces and complete anesthesia of the trunk below the nipple line and of the legs. The intrinsic muscles of both hands showed wasting and other signs of atrophy of the lower motor neuron. An ascending urinary infection developed.

Examination of the cerebrospinal fluid revealed Froin's syndrome, a marked globulin reaction and 3 cells per cubic millimeter. The Wassermann and Kahn

54. Dickson, W. E. C., and Hill, T. R.: Malignant Adenoma of the Prostate with Secondary Growths in the Vertebral Column Simulating Pott's Disease, Brit. J. Surg. **21**:677 (April) 1934.

reactions of the spinal fluid were negative. Roentgenograms revealed a collapse of the bodies of the seventh cervical and the first thoracic vertebra, and crushing of the three contiguous intervertebral disks, which almost touched each other. There was rarefaction of the body of the second thoracic vertebra and of the transverse processes of the first and second thoracic vertebrae on the right side, as well as of the heads and necks of the first and second ribs on the right side. The roentgenologic findings suggested Pott's disease, with vertebral collapse from softening.

The patient died suddenly, and at necropsy the bony changes were found to be caused by metastatic carcinoma.

The primary tumor was found to involve the prostate, which was only slightly enlarged and the seat of a malignant adenoma.

The case is of interest because of the age of the patient, the silent primary prostatic tumor, the early malignacy in an adenoma, the clinical picture of a tumor of the spinal cord and the roentgenologic findings suggesting Pott's disease.

The bony metastasis was completely osteoclastic and did not show any evidence of the osteoplastic process which is generally described as characteristic of metastasis of a malignant tumor of the prostate to the bones.

Lowsley and Kimball [55] reviewed the literature of sarcoma of the prostate and reported a case of this condition.

The patient was 64 years of age and was admitted to the hospital because of painful and frequent urination and dribbling, which had been present for three years and had increased in severity. Rectal examination revealed a flat prostate, which was of leathery consistency and about two and a half times the usual size. A diagnosis of adenomatous hypertrophy was made, and a suprapubic cystostomy for drainage disclosed a moderate intravesical intrusion. The second stage was not done because of renal insufficiency, and the patient was dismissed from the hospital but was kept under observation for four months, during which time there was no improvement in function of the kidney. He was readmitted to the hospital when it was found that there was an enormous intravesical intrusion of the median portion of the prostate. Excretory urography demonstrated an advanced right hydro-nephrosis and hydro-ureter. There was no excretion of mediums, hence an absence of renal function on the left side. Removal of the prostate was not attempted, and the patient died of uremia two months later.

The anatomic diagnosis at necropsy was leiomyosarcoma of the prostate, bilateral pyonephrosis and bronchopneumonia.

The 132 cases of sarcoma of the prostate which had been reported previously were reviewed and analyzed. Prostatic sarcomas are common to all ages, although 35 per cent occur before the age of 20 years. In young patients, the course is rapid, but when this tumor affects adults, the course is slower, the average duration being nine months. Pain is a prominent symptom. The tumor may grow to an enormous size and cause complications by pressure. Because of its softness, which at times may produce fluctuation, the tumor may suggest a prostatic abscess.

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55. Lowsley, O. S., and Kimball, F. N.: Sarcoma of the Prostate, Brit. J. Urol. **6**:328 (Dec.) 1934.

The tumor invades the bladder, seminal vesicles and rectum, and metastasizes by both the lymphatics and blood stream to the kidneys, inguinal lymph nodes, lungs, liver, pleura and spleen, in this order of frequency.

The disease is invariably fatal, and treatment should be limited to roentgenotherapy and radium therapy to control pain.

Blood Supply.—Bumpus and Antopol [56] said that the supply of blood to the prostate gland may be divided into three definite zones: (1) the peripheral plexus of small arteries; (2) an intermediate zone of essentially parallel vessels coursing toward the urethra, where they anastomose to form (3) a zone in which a periurethral or internal plexus is formed. It is evident that in performing transurethral resection the third zone of vessels will be encountered first; they are of large caliber and anastomose so freely about the entire circumference of the urethra that there is no single point at which the bleeding can be entirely controlled. Because of the size and extensive anastomosis of these vessels, bleeding will be more profuse in the periurethral zone than in the deeper, intermediate zone. From a case in which examination was made after operation, it appears that the destruction of the supply of blood may extend well toward the peripheral zone.

PENIS

Carcinoma.—Horn and Nesbit,[57] in discussing tumors of the penis, said that circumcision in infancy is to be recommended. Early circumcision should be done in all cases of sclerosing balanoposthitis. In all cases in which middle-aged or older persons have been subjected to this procedure and the wound does not heal promptly or within a reasonable length of time, the condition should be regarded as potentially malignant and treated accordingly. The type of operation to employ in the treatment of carcinoma of the penis depends on the nature of the lesion. Radical resection of the regional lymph nodes need not be a routine procedure, even in cases in which there is enlargement of these nodes, because in a great many cases the enlargement is not the result of metastasis but of infection. Emasculation is indicated only in cases in which there is extension to the scrotum or its contents.

Graves [58] said that partial amputation of the penis for carcinoma may be done by any standard method, but the line of incision should be at least 2 cm. proximal to any palpable thickening in the region of the

56. Bumpus, H. C., Jr., and Antopol, William: Distribution of Blood to the Prostatic Urethra: A Demonstration, J. Urol. **32**:354 (Oct.) 1934.

57. Horn, K. W., and Nesbit, R. M.: Carcinoma of the Penis with Report of 37 Cases, Ann. Surg. **100**:480 (Sept.) 1934.

58. Graves, R. C.: Treatment of Malignant Disease of the Penis, Tr. Am. A. Genito-Urin. Surgeons **27**:421, 1934.

growth. The stump of the urethra should be left longer than the stump of the corpora cavernosa; the actual division of the latter is done more satisfactorily with high frequency current. Coagulation controls hemorrhage and lessens the possibility of the dissemination of cells of the tumor.

The technic which Graves used in the treatment of advanced and dangerous lesions is as follows:

There should first be a period of supportive medical care, varying in duration and character with the needs of the individual case. Spinal anesthesia usually is obtained with procaine hydrochloride. Unless the groins are to be dissected, the patient is placed in the position for lithotomy. A vertical suprapubic incision is made in the median line. This extends upward sufficiently so that the scrotum will be drawn well away from the perineum when its upper portion is attached to the apex of this wound at the end of the operation. The lower pole of the incision reaches the base of the penis, where it encircles the organ and penetrates as far as the actual fibrous sheaths of the corpora cavernosa and spongiosum. The corpus spongiosum is then cut across with the high frequency knife, well proximal to the tumor and at a level which will allow sufficient length of the urethra into the perineum for transplantation without tension. A soft bougie then is passed into the open urethra. This aids in dissecting the corpora spongiosum away from the corpora cavernosa. The corpus spongiosum must be freed until it can be brought straight through a small stab wound in the perineum, between scrotum and anus, without angulation or tension. Moist gauze and a wooden spatula are placed between the roots of the cavernous bodies and the bulb to prevent injury of the urethra when the corpora cavernosa are finally amputated near their attachments, with a mildly coagulating current. The open ends of the stumps are closed, either separately or together, with a continuous lock suture of chromic catgut. The stump of the urethra should protrude at least 1 cm. beyond the skin of the perineum at the end of the operation; any redundant portion is cut away. A wick of iodoform gauze is left in one angle of the upper wound for temporary drainage, and the cut edge of the scrotum in the median line is approximated to the apex of the suprapubic incision. Finally, a small soft rubber catheter usually is passed to the bladder and lightly secured to the urethra with a stitch of fine silk or catgut, for the first few days.

The dressings are an important feature of the postoperative care. There always should be a roll or pad in the perineum, in front of the urethra. This is held firmly in place by a perineal binder. It obliterates the newly opened space in the region back of the scrotum and, by elevating the scrotal wall, serves also to protect the suprapubic suture line from undue tension. Whether the inguinal regions are dissected at the time of the amputation of the penis, or at a second operation, the dissection is done through an incision which begins medially to the anterior superior spine and extends parallel with, and above, Poupart's ligament, to within about 1 fingerbreadth of the spine of the pubis, where it curves downward and outward across the femoral triangle. This affords a more adequate exposure than does a simple oblique incision in the groin, and it avoids the poorly healing corners of a T-shaped wound. All palpable lymph nodes and the fat which contains the lymph nodes are removed en masse as far medially as the spermatic cord and the external ring. The dissection must be carried downward over the thigh also, for in Graves' experience a lymph node often is found much farther distally

along the saphenous vein than is expected. A segment of this vein usually will be included in the mass which is removed. Special care must be used to dissect the inner aspect of the femoral vein and the region leading into the crural canal.

High voltage roentgenotherapy directed to the femoral, inguinal and deep pelvic regions should be used in all cases following surgical dissection and in those cases in which, for some reason, such dissection has not been undertaken.

URETHRA

Stricture.—Young [59] said that it frequently is necessary to pass dilating instruments after various operations which involve the urethra, such as those which are employed for the relief of trauma, inflammatory strictures, urinary incontinence or congenital defects of the urethra. Difficulty may be encountered in passing filiforms through the dense stricture, particularly as they have a tendency to buckle on themselves and prevent the passage of a dilator; the attempt to pass some such dilator often may lead to severe traumatism, if the operator does not realize that the filiform has buckled and broken. New instruments and technical methods which eliminate these difficulties are described. These include a series of urethral tubes which facilitate the discovery of the urethral lumen in the strictured area and also prevent the buckling of the filiform when it and the attached dilator are passed. The use of the catheterizing cystoscope to dilate a stricture of the deep urethra by passing filiforms backward is described. Also various technical devices for joining one filiform to another or for attaching a silk thread or a piece of silkworm gut which is to be left in place to conduct other filiforms through the strictured region at subsequent times are depicted. By means of these mechancial devices, the postoperative care of various urologic patients has been rendered more accurate and satisfactory than it has been in the past.

Caulk [60] reported a series of 1,495 cases of stricture of the urethra. In only 52 of these cases was urethrotomy required; in 2 of these cases the stricture was internal and in 50 cases it was external. In this number of cases, only 2 internal and 10 external urethrotomies were done for uncomplicated stricture, 5 of these having been done prior to 1913. The remaining number were performed for complications associated with stricture, such as extravasation of urine, periurethral abscess, fistulas and impassable stricture. In only 0.8 per cent of all the cases was operation resorted to for simple uncomplicated stricture.

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59. Young, H. H.: New Methods of Dealing with Difficult Strictures of the Prostato-Membranous Urethra, Tr. Am. A. Genito-Urin. Surgeons **27**:19, 1934.

60. Caulk, J. R.: External Perineal Urethrotomy with Invagination and Resection of an Impermeable Stricture of the Penile Urethra, Tr. Am. A. Genito-Urin. Surgeons **27**:351, 1934.

Caulk [60] reported a case in which there was an impassable stricture of the penile portion of the urethra. Internal urethrotomy was impossible, since no fluid could be introduced, and external urethrotomy at this site was to be avoided. An external perineal urethrotomy was therefore performed.

The bulb was opened in its anterior portion, after the posterior portion of the scrotum had been bisected. The bulbous urethra at this point was tremendously dilated, being at least an inch in diameter; this later aided localization of the stricture. A sound was passed through the external meatus to the stricture at the penoscrotal juncture. It was then pushed backward until the obstruction could be seen through the dilated urethra from above. The circular scarred region was then grasped with Allis clamps and invaginated into the bulbous urethra; the sound was gently pushed from the front to aid this maneuver. The segment which was the site of the stricture was then incised vertically until the sound could be passed through it. It was almost a quarter of an inch in breadth. It was then resected circularly until the annular band was completely removed. Before excising this segment completely, the urethral mucous membrane was grasped above and below the sound with Allis forceps, and while the affected segment was being resected, the proximal and distal ends of the urethra were approximated with sutures. Before the sutures were tied, the sound was removed and a no. 24 catheter was passed through the site of the stricture. The sutures were then tied, and a catheter was passed into the bladder for drainage and splinting. After the redundant tissue had been removed, the urethra was closed over the indwelling catheter with interrupted sutures of chromic catgut. A small rubber tissue drain was inserted, and the skin and fascia were closed. The suprapubic catheter was removed and the sinus curetted. The operation was simple in spite of the dense scar tissue. It was not difficult to invaginate the penile urethra into the perineal incision by traction and pressure without mobilization of the urethra through external dissection. The recovery was uneventful.

BARTHOLIN'S GLAND

Carcinoma.—Lyle [61] expressed the opinion that carcinoma of Bartholin's gland is as malignant as epithelioma of the vulva and, unfortunately, is also resistant to the roentgen rays. He said that the primary operation should consist of a wide excision of the vulva and a secondary dissection of the inguinal and femoral lymph nodes. The excision should be carried out with the cold scalpel or the endothermic knife. In the advanced cases, it is advantageous to destroy the original growth with endothermic coagulation and then proceed immediately with resection. The operation should be followed by thorough local and regional irradiation. Healy, in his cases, applied radon seeds to the recurrence and later did a radical excision of the regional lymph nodes. The success of any method rests on an early diagnosis; this diagnosis is not hard to make if the condition is kept in mind.

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61. Lyle, H. H. M.: Primary Carcinoma of the Bartholin Gland, Ann. Surg. **100**:993 (Nov.) 1934.

ANURIA

Joly [62] said that anuria is a symptom of a number of diseases, some of which are primarily unconnected with the urinary tract; it should never be considered as a disease itself. The conditions which cause anuria are so numerous that cases in which this symptom is exhibited are usually classified in three groups: The first one comprises cases in which the abolition of the excretion of urine is the result of some general cause, usually a change in the circulation of the blood. Advanced cardiac disease, a marked fall of the blood pressure or a local interference with the renal circulation are examples of this type, which is known as prerenal anuria. The second type is a renal anuria, and is caused by some change in the renal parenchyma which renders it incapable of excreting urine, poisoning with corrosive mercuric chloride being the most typical example. In the third group, the urine is dammed back in the urinary passages so that none of it can escape; this form is called postrenal or obstructive anuria.

Cases of unilateral anuria are not infrequent. One kidney is completely obstructed by a calculus, but the condition is disguised by the continued secretion from the opposite organ. It is important to recognize these instances, as improvement in the condition of the obstructed kidney depends on prompt removal of the calculus. Unrelieved obstruction always results in the death of the kidney. There are two types of complete anuria which complicate lithiasis: The first is the obstructive type, in which the cessation of excretion is primarily the result of the mechanical action of a stone or stones which block the urinary passages. This form is commonly called calculous anuria. In the second type, there is no obstruction, but the renal parenchyma is so damaged by the presence of calculi, which usually are associated with sepsis, that it is no longer capable of excreting urine. In cases of this nature, the anuria usually is terminal, is unaffected by treatment, and is preceded by a long period in which the patient shows signs of renal failure. Calculous anuria is the most important type of complete anuria occurring with lithiasis, as it is amenable to treatment. The kidneys are not destroyed, but excretion is inhibited, and the kidneys can resume their function once the obstruction is removed. Cases of calculous anuria may be divided into three groups, according to the nature of the obstruction: obstruction of both kidneys or ureters, obstruction of the only functioning kidney and unilateral obstruction. The chief interest in unilateral obstruction is focused about the state of the unobstructed kidney and the reason why it has ceased to function. Formerly, many

62. Joly, J. S.: Anuria as a Complication of Lithiasis, Tr. Am. A. Genito-Urin. Surgeons **27**:209, 1934.

cases were described in which the unobstructed kidney was supposed to be healthy, on insufficient grounds. If no stone was found, the organ was assumed to be healthy.

The common and extensive use of the term "reflex anuria" tends to overshadow the fact that the condition depends on the existence of a reflex arc from one kidney to the other, and on whether the unobstructed kidney is inhibited through the nervous mechanism or in some other way. The discussion of reflex anuria has lasted for more than forty years, and as yet there is no consensus. It is now generally accepted that the excretion of urine is essentially a double process: filtration and selective absorption.

Joly was of the opinion that complete anuria following obstruction of one kidney may be explained on the assumption that it is a result of diminution in the general blood pressure, and that a comparatively slight decrease is sufficient when the unobstructed organ is diseased, but a much larger decrease is necessary if it is healthy. This is offered as an alternative to the theory of reflex anuria.

In the cases in which anuria is accompanied by stone, the anuria usually is terminal and is ascribed to renal failure. It is similar to the terminal anuria of chronic pyelonephritis and similar conditions. In these cases there usually is a prolonged febrile period, during which, although a fair quantity of urine is eliminated, the amount of urea in the blood increases slowly, and the usual signs of uremia appear. This is followed by a short period, usually from two to three days, in which the temperature suddenly drops to subnormal, and suppression of urine supervenes. Suppression generally is attributed to renal failure, but in all the cases observed by Joly, it was preceded by a marked decrease in blood pressure. He believed that the suppression is caused by heart failure, and that the treatment should be directed toward reestablishing the circulation. At present, attempts are made to stimulate the kidneys, and this line of treatment always fails. Joly was of the opinion that this form of anuria is caused by circulatory failure, and that it is, therefore, prerenal.

Hinman [63] stated that anuria in the presence of obstruction is commonly explained as either the result of retention, as in cases in which there is complete obstruction, or of cessation of secretion, as in cases of the reflex type, in which there are spasm of the blood vessels and anuria of the secretory type. In experimental work with animals, there are two distinct pathologic changes with complete obstruction of the ureter: In one, there is anuria at the onset, also primary atrophy. In the other, in which there is not anuria, hydronephrotic atrophy occurs.

63. Hinman, Frank, in discussion of Joly,[62] p. 230.

Hydronephrosis cannot develop with anuria. Therefore, in cases in which complete obstruction of the ureter and hydronephrotic atrophy are present, there is not anuria but retention.

An interesting type of anuria from obstruction in the tubules occurs in association with hemoglobinuria. The hemoglobin crystals, which are precipitated in the blood or in the tubules after the urine is secreted, block the tubules and produce obstruction and anuria. The recognized treatment in these cases is to give large doses of alkali, which dissolves the hemoglobin crystals and reestablishes the urinary secretion.

CARCINOMA STATISTICS

Duff [64] reported that all forms of carcinoma caused 125,740 deaths among the industrial policy-holders of the Metropolitan Life Insurance Company, who were aged 1 year or more, in the twelve year period from 1917 to 1928. When related to the more than 174,000,000 years of life recorded for these policy-holders, the mortality was 72.2 per hundred thousand.

Carcinoma of the bladder caused 3,315 deaths, 2.6 per cent of the total deaths from all types of carcinoma in this twelve year period. A higher mortality from carcinoma of the bladder was registered for white males (2.6) than for white females (1.5). The higher rate for males was in evidence at each significant age period. Among the colored race, the males showed a higher mortality than the females; the rates were 2 and 1.3, respectively. White men suffered a higher mortality than did colored men, but among women the element of color was insignificant. The death rate from carcinoma of the bladder rises continuously with advancing age; practically no deaths occurred from this lesion among persons under 25 years of age.

Carcinoma of the prostate caused 1,904 deaths in these twelve years. This is only 1.5 per cent of the deaths from all malignant growths. The death rate for white and colored males was identically the same (2.5 per hundred thousand). The mortality from this disease also rises with increasing age, but the mortality is not significant before the age of 55 years. The mortality at the various age periods for white persons was close to that registered for colored persons. The trend of the death rate from carcinoma of the prostate appears to be upward since 1917. Among colored males the increase was considerably more than it was among white males.

The death rate from carcinoma of the kidneys and suprarenal glands in the period from 1917 to 1928 was 0.8 per hundred thousand. The number of deaths was 1,332, or 1.1 per cent of the entire mortality from

64. Duff, John: Cancer Mortality: Bladder, Kidney and Prostate, 1917 to 1928, J. Urol. **32**:346 (Oct.) 1934.

carcinoma in this period. Of the 1,332 deaths, no less than 313 (23.5 per cent) were those of persons between the ages of 1 and 25 years. The death rate at this age period was 0.3 per hundred thousand. The figures for the different sexes show little difference. The death rate for white persons of each sex is practically double that for the colored. The age curve differs from the usual carcinoma curve in that no rise is shown between the earliest age group and the one following (from 25 to 34 years); also, the rise with increasing age is not as sharp as for most types of carcinoma. In general, the frequency of this type of carcinoma in the last five years of the period appeared to have changed relatively little in comparison with that for the preceding five years.

ANESTHESIA

Jeck [65] reviewed a series of cases in which spinal anesthesia was induced with nupercaine in the low dilution of 1:200, and compared this with a series of cases in which a dilution of 1:1,500 was employed. Satisfactory anesthesia was induced with the weaker solution in 90 per cent of the cases and with the stronger solution in 68 per cent of the cases. In a group of operations below the umbilicus, in which practically any spinal anesthetic would have given relatively satisfactory results, the percentage of successful anesthesias with the dilute solution was slightly higher than that with the concentrated solution.

Vomiting, headache and distention occurred about equally after the use of the concentrated and dilute solutions of nupercaine. Vomiting depends on the level to which the anesthetic extends. This is substantiated by the fact that in the operations above the umbilicus vomiting occurred in a third or more of the cases in which either the concentrated or the dilute nupercaine solution was given; the percentage of cases in which vomiting occurred was slightly higher with administration of the dilute solution than with that of the stronger solution. Headache, one of the most troublesome of the sequelae of spinal anesthesia, is not encountered any more frequently after spinal anesthesia induced with nupercaine than after that produced with other drugs.

With both the dilute and the concentrated solutions of nupercaine, the respirations are usually shallow and regular; respiratory failure is an ever present danger. If respiratory failure occurs, a mixture of carbon dioxide and oxygen should be forced into the lungs by means of an inhalation apparatus. Respiratory failure is less likely to occur from phrenic paralysis than from fatigue of the respiratory center, which is caused by the anoxemia resulting from imperfect pulmonary ventila-

65. Jeck, H. S.: Nupercain as a Spinal Anesthetic with Special Reference to the Employment of Nupercain Solution of High Dilution, Tr. Am. A. Genito-Urin. Surgeons **27**:411, 1934.

tion, which, in turn, is the result of temporary paralysis of most of the intercostal muscles. The administration of carbon dioxide and oxygen should rapidly restore regular breathing, unless the respiratory center has already been paralyzed by large doses of morphine, tribromethyl-alcohol (avertin) or similar drugs.

POSTOPERATIVE HEMORRHAGE

Weil [66] said that it is of the greatest importance to the urologic surgeon to determine, before undertaking an operation, the tendency of the patient to bleed. If, instead of the usual bleeding, a massive hemorrhage occurs, the patient's blood is at fault. Hemorrhages can be prevented, since most abnormalities of the blood can usually be corrected. To this end Weil proposed four methods of investigation:

1. A study should be made of the coagulative qualities of the blood in vitro (method of Hayem). In this test the blood is always taken from a vein at the elbow and not drawn from the tissues; this prevents possible contamination that might interfere with coagulation and thus obscure the true facts. The examination should reveal whether coagulation is normal, retarded, diminished or absent. The color of the serum should be observed, and the retractile function of the coagulum and possible autolysis should be noted.

2. The number of platelets should be determined (method of Pagniez and Lesourd), as well as the proportion of platelets in comparison to the erythrocytes. This interesting test may be omitted, however, since the other three tests are sufficient.

3. A study should be made of the purpura that is produced experimentally by the tourniquet test (as described by Frugoni of Italy and by Weil and Chalier of France). In cases in which there is weakness of the capillaries, petechiae remain; that is, the tourniquet test is positive. It is absent, however, in cases of hemophilia.

4. The duration of experimental bleeding should be determined (as described by Duke). The size of the drops received on filter paper also should be observed. In cases in which the blood is normal, the size of the drops diminishes after a known time. In cases in which there is a hemorrhagic tendency, the size varies and the rhythm of the drop is entirely irregular. Coagulation, if excessively retarded, is conclusive proof of hemophilia, which is always accompanied by diminished retractibility of the coagulum and by plasmatic coagulation. The provocation of purpura by arrest of venous circulation, the irretractility of the coagulum and the marked diminution of platelets form a characteristic syndrome of

66. Weil, P. E.: Les hémorragies post-opératoires: Comment les prévoir et les prévenir? J. d'urol. **38**:289 (Oct.) 1934.

pathologic hematogenesis. It is, of course, possible, even in the presence of abnormal function of the blood, that not all tests are indicative of the disturbance; one test may be negative. This depends partly on the nature of the disturbance and partly on the general state of the patient. The causes of a tendency to bleed are:

1. Hemophilia, a rare disease, which usually is inherited, but may appear sporadically and affect persons who are not members of hemophilic families. In either case, the hemorrhage is the result of provocation, although the hemorrhage is less serious in the sporadic cases.

2. Hematogenesis, which has frequently been confused with hemophilia. It differs from the latter in that the hemorrhage may be provoked, or, again, it may be spontaneous. These subjects show weakness of the capillaries, prolonged duration of bleeding and troubles of coagulation without notable retardation of coagulation.

3. Hepatism, which is prone to affect patients and gives the same signs as vascular disease does. Knowing the cause of these signs to be disease of the liver, and less serious than diseases of the blood vessels, the surgeon may, however, anticipate the possibility of hemorrhage and act accordingly. The clinical examination, the history and the tests which have been described will reveal whether or not a patient possesses a tendency to bleed. Weil has shown that postoperative hemorrhages are preventable. For almost thirty years, he has demonstrated that the inability of coagulation in hemophilia can be corrected in vitro by the action of serum, and that retarded coagulation can be corrected in vivo by injection of serum. Such injections of serum have not proved satisfactory in the treatment of other conditions, because of the possibility of anaphylaxis. In the treatment of these conditions hematotherapy gives excellent results. In the evening before the operation, from 10 to 15 cc. of blood should be injected subcutaneously, without regard to different groups of blood. This treatment is sufficient in nearly all cases. In the presence of hemophilia, however, a transfusion of about 300 cc. of blood from a universal donor, or from a donor belonging to the same group, is recommended. This preparatory hematotherapy gives assured results. No other method is as satisfactory. If there is time, calcium may be prescribed for a long period; this will lessen capillary weakness. It is not to be regarded as a substitute, however, but merely as a complement to the methods described before, which give to the surgeon the means of successfully preventing postoperative hemorrhages.